PEPIJN BISSELING

HIP RESURFACING: PERCEPTIONS AFTER THE STORM

HIP RESURFACING: PERCEPTIONS AFTER THE STORM

Pepijn Bisseling

The publication of this thesis was kindly supported by:

Radboud Universiteit Nijmegen
Nederlandse Orthopaedische Vereniging
Stichting OrthoResearch
Vakgroep Chirurgie en Orthopedie Rijnstate Ziekenhuis
Stöpler Instrumenten en Apparaten B.V.
Bauerfeind Benelux B.V.
Anna Fonds|NOREF

Colofon

Author:	Pepijn Bisseling
Cover design en lay-out:	Miranda Dood, Mirakels Ontwerp
Printing:	Gildeprint - The Netherlands
ISBN:	978-94-92380-07-4

HIP RESURFACING: PERCEPTIONS AFTER THE STORM

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op vrijdag 6 januari 2017
om 12.30 uur precies

door

Pepijn Bisseling

geboren op 21 oktober 1983
te Ede

Promotor

Prof. dr. A. van Kampen

Copromotor

Dr. J.L.C. van Susante (Rijnstate Ziekenhuis)

Manuscriptcommissie:

Prof. dr. C.G.J. Sweep

Prof. dr. W.M. Prokop

Prof. dr. R.G.H.H. Nelissen (LUMC)

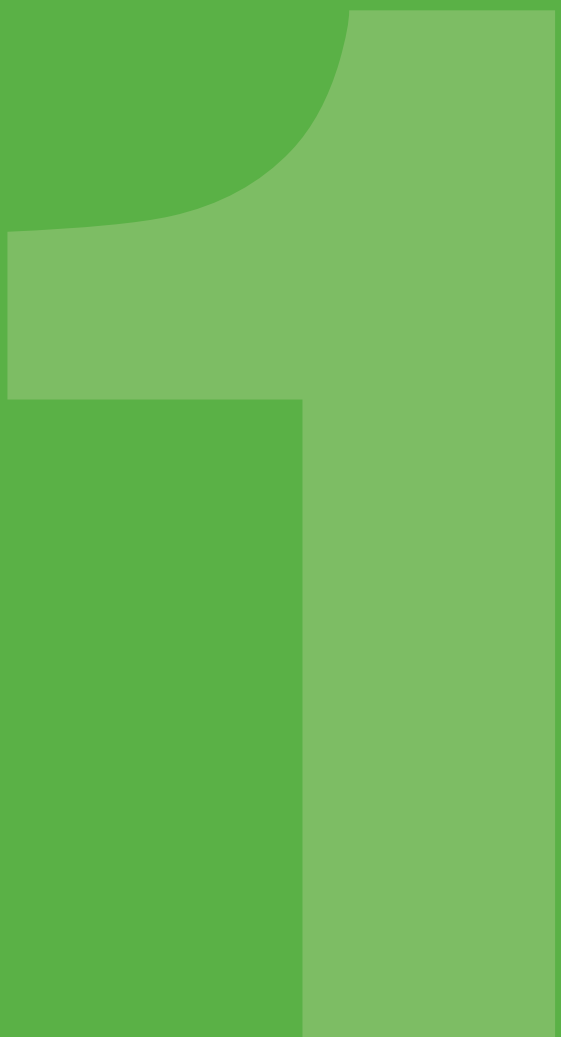
TABLE OF CONTENTS

APTER 5 Metal ion levels in pa
total disc replacement. Shou
J Bone Joint Surg [Br] 2011;93-B:9

APTER 6 Similar incidence of periprosthetic fluid
ceramic-on-polyethylene total hip arthropl
on-metal resurfacing arthroplasties.
one Joint Journal. 2015;97-B:1175–82.

CHAPTER 1

Introduction



INTRODUCTION

Osteoarthritis is a degenerative joint disease with a high and increasing prevalence. In 2011, the prevalence of osteoarthritis in the Netherlands was 53.8 per 1,000 men and 88.5 per 1,000 women and it is predicted that this number will increase by approximately 140% between 2011 and 2030.[1] The increase of osteoarthritis can be related to general demographic changes, increase in the incidence of overweight and obesity, and more active lifestyles of elderly people. Osteoarthritis can have a major effect on quality of life and social-economic functioning in relatively young and active patients in particular. Patients may have difficulties in their work and become dependent on their environment and healthcare facilities. The costs of osteoarthritis are estimated to be around €1.1 billion each year for a small country, such as the Netherlands.[1] With increasing prevalence of osteoarthritis globally, this can be considered as a serious burden to society.

While the most commonly affected joint is the knee, the second most common form of osteoarthritis is osteoarthritis of the hip.[1] Initial treatment regimens for osteoarthritis of the hip are generally conservative, but when this fails, a total hip arthroplasty is indicated in patients with advanced osteoarthritis. Total hip arthroplasty is a frequently performed and cost-effective procedure with a successful clinical outcome that improves quality of life and social-economic functioning of many patients.[5,6] In 2014, 28,026 primary total hip arthroplasties were performed in the Netherlands, and the trend projection suggests an increase of 140% towards 2030.[7-9]

The success of total hip arthroplasties in older patients caused an extension of its indication to young- and more active patients due to good long-term results compared to hip-preserving treatments.[11] However, young and active patients that present for total hip arthroplasties hope to restore their quality of life, which apparently differs from those of elderly, and typically includes physically demanding activities. Consequently, the long-term results in young and more active patients are less successful with a lower overall survival.[12,13] The history of hip arthroplasty is still dynamic and innovations are directed at reduction of failure, especially in younger patients with a higher activity profile.

Figure 1. Smith-Peterson Vitallium® mould (cobalt–chromium–molybdenum alloy) arthroplasty interposed between refashioned surfaces of acetabulum and femoral head.[3]

The history of total hip arthroplasty dates back to the first half of the 20th Century. At that time, the first efforts were made to treat patients with osteoarthritis through interposition of soft tissues, such as the fascia lata, skin and mucosa of a pig bladder, all with poor results.[14] The search for an inert material that could be successfully interpositioned started in 1923. Since then, Smith-Peterson experimented with glass mould and other substances, as an interposition in the hip. However, these materials could not sustain the forces that they were exposed to, and broke within a matter of months after implantation. Fifteen years passed until Smith-Peterson introduced a new arthroplasty that used a vitallium mould to cover the femoral head (figure 1). While the results were still poor, they were recorded to be more satisfactory than an arthrodesis of the hip.[15]

In the meantime, Wiles developed the first prosthetic total hip replacement. In 1938, he tried inserting a pre-formed acetabulum and femoral head, both made of stainless steel (figure 2A).[2] This prosthesis can be regarded as a prototype for the modern type of total hip arthroplasty, and the first metal-on-metal implant. Thereafter several metal-on-metal implants, such as the McKee and Watson Farrar Prosthesis, were developed, but all failed due to poor material and failure of fixation (figure 2B).[4]

Innovations in total hip arthroplasty continued, and a major advance was made in the 1960s, when Sir John Charnley introduced a low-friction torque total hip arthroplasty (figure 2C). He used a 22mm metal head and a polyethylene socket and fixed the components to the bone with a filling methacrylate bone-cement.[10] The survival of this prosthesis was very good and has been reported to be approximately 81-85% at 25-years follow-up. Even for modern designs, this survival rate is high and can be considered as the golden standard.[12,16]

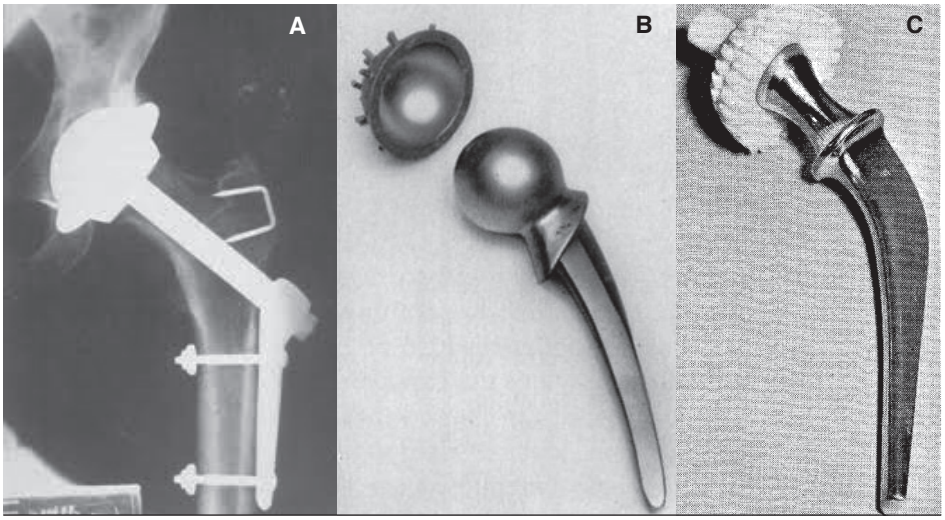


Figure 2.
(A) Wiles metal-on-metal total hip arthroplasty.[2]
(B) McKee-Farrar metal-on-metal total hip arthroplasty.[4]
(C) Charnleys' low friction total hip arthroplasty.[10]

One of the main causes of failure of the Charnleys' total hip arthroplasty was loosening, as a result of mechanical failure of fixation.[14] Although new materials and improved cementing techniques reduced the rate of loosening, loss of fixation was still seen, especially in young and active patients.[17,18] At first, it was associated with an inflammatory response to particles from the bone cement, referred to as 'cement disease'.[19] New implants that used cementless fixation were developed. Nevertheless, lytic lesions were still reported in stable uncemented implants.[20] Fragments of polyethylene wear were now recognised as the causative factor of premature loosening by periprosthetic bone-loss secondary to particle-induced osteolysis.[21] Surfaces of articulating surfaces are prone to wear, and subsequently release small particles. These particles are phagocytosed and initiate an inflammatory response. The process of particle-induced osteolysis is complex and involves the interaction of various cell types, cytokines, chemokines and growth factors that stimulate osteoclast differentiation and activation, which results in osteolysis.[22]

The biologic effects of wear debris are an important factor that limits the longevity of total joint replacements. Nowadays, a total hip arthroplasty with a ceramic head and a

polyethylene acetabular component is common practice in the Netherlands (54%), with metal-on-polyethylene arthroplasty (30%) as the second most frequently used combination.[7] Both combinations use a polyethylene acetabular component that has limited wear properties. This is especially important for young and active patients, in which higher stresses on the bearing may enhance wear and induce premature aseptical loosening. The introduction of highly cross-linked polyethylene and the addition of Vitamin E might have overcome the problem of wear of the conventional type of polyethylene, but this is still uncertain since long term studies are limited.[23,24] The search for new, durable materials that can minimise wear and improve the longevity continues, as does the development of alternative surface bearings, including metal-on-metal bearings and more recently introduced, ceramic-on-ceramic bearings.

The use of metal-on-metal bearings is not new and dates back to the beginning of the development of total hip arthroplasties.[2,4] Above all, the name McKee is associated with the first generation metal-on-metal implants, but many others, including K.M. Sivash, P. Ring, J. Scales, A. Hugler, M. Müller and M. Postel, were involved.[25] The first generation had a high rate of component loosening, which in retrospect, cannot be contributed to the wear of the metal-on-metal articulation, but rather unfavourable biomechanics and the role of the implantation technique.[26] However, the promising results of the Charnley hip prosthesis diminished interest in metal-on-metal bearings during the 1960s and 1970s. Renewed interest arose in the 1980s, when premature loosening was related to polyethylene wear-induced osteolysis. It was recognised that debris-induced osteolysis featured less frequently in the first metal-on-metal hips, due to a lower wear-rate compared to polyethylene. This initiated the introduction of the second- and third generation metal-on-metal implants that used alloys with a higher carbon content (0.20 - 0.30%), with a hardness that would enable precise manufacturing. In addition, joint movements were optimised by smoother bearing surfaces.[25] Implant retrieval studies revealed superior wear, characteristic in the region of five microns a year, which is a decrease of about a 60-fold compared to polyethylene.[27,28] This would, in fact, reduce particle-induced osteolysis, and prolong implant survival. Another advantage of metal is its self-polishing characteristic, and hardness, although not brittleness. This has created the opportunity to design prostheses with thin acetabular components and large femoral heads.

Creating a thin acetabular socket also enables the creation of a femoral bone-reserving option; a resurfacing hip arthroplasty. McMinn was the first to combine the experience with metal-on-metal implants with the hip resurfacing concept, and introduced it in the 1990s.[29] The concept of a resurfacing hip was not new. In the 1970s, the first generation of a resurfacing concept, the Total Hip Articular Replacement using Internal Eccentric Shells (THARIES) hip replacement was introduced.[30] The THARIES consisted of a thin polyethylene acetabular component and a metal femoral cap. Failures of this hip replacement were primarily related to the very thin acetabular component.[31] The implant was abandoned by the mid-1980s due to its high failure rate in comparison with total hip arthroplasties.

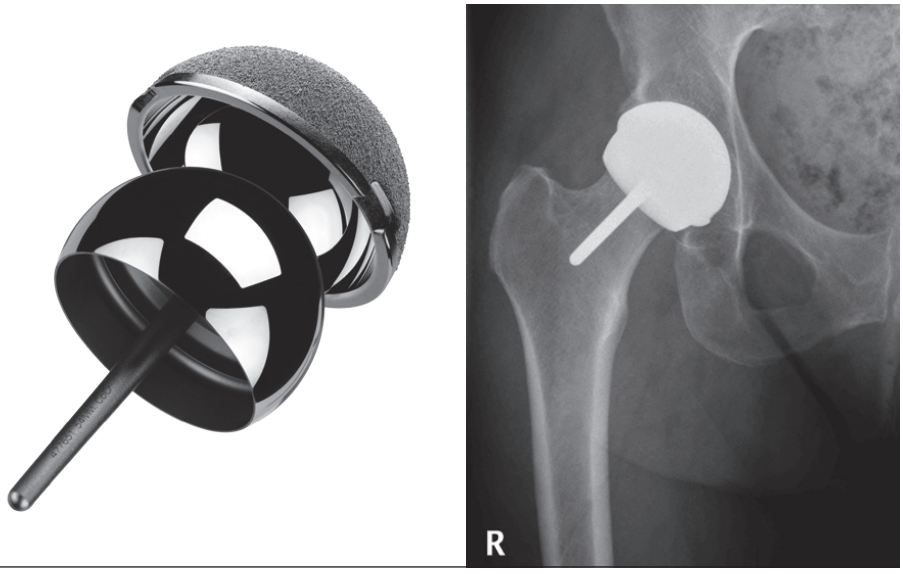


Figure 3. Resurfacing hip arthroplasty. Conserve plus® (Wright Medical Technology, Arlington, Tennessee, USA)

Although the conventional design total hip arthroplasty was favoured in clinical outcome, the aim for a resurfacing implant persisted. The bone- and natural anatomy preserving characteristics of resurfacing remains an appealing treatment option, especially for young and active patients. In the 1990s, the resurfacing hip arthroplasty was reintroduced and marketed as the latest advancement in hip arthroplasty. The theoretical advantages and

clinical results addressed in the initial clinical studies were appealing.[32-34] In addition, in vitro studies revealed superior wear characteristics, with up to 100-fold reduction of wear debris compared to metal-on-polyethylene.[35] Moreover, the resurfacing technique preserves the bone of the proximal femur and leaves the option to perform a 'primary' total hip arthroplasty at times that the resurfacing hip arthroplasty fails. The wear characteristics and additional revision options are not the only factors that make the resurfacing implant attractive for young patients. Theoretically, the use of a larger femoral head diameter compared to a conventional design of hip arthroplasty also has a substantial effect on the stability of the hip.[35,36] Pushing the hip further than the maximum arc, in which the neck impinges on the socket, will lift the head out of the socket. The distance before the head can escape the rim of the socket is called the 'jump distance'. A larger head increases the jump distance and positively affects the stability of the hip, which subsequently lowers dislocation rates.[36-38]

Based on the proposed theoretical advantages, the resurfacing hip arthroplasty was promoted as an attractive alternative for the conventional total hip arthroplasty. The name 'sports hip', as it was called in the Netherlands, sounded appealing to patients compared to the conventional type of implant that was generally related to the older, inactive patient. In particular, young patients with hip osteoarthritis were intent on having a resurfacing hip implant. Globally, the increased demand led to an accelerated introduction of various resurfacing hip implants on the market and a rise in their use.[39] However, long-term clinical results of these implants were lacking. The potential disadvantages, such as the more technical demanding procedure, the subsequent potential risk of femoral neck fractures, the occurrence of excessive metal ion release, and adverse reactions to metal debris (ARMD), were less widely specified and, in hindsight, may have been underestimated.[40-44]

Aim of this thesis

In a time of rapidly emerging market of resurfacing hip arthroplasties, a randomised clinical trial was initiated, in which the new concept of resurfacing hip arthroplasty was balanced against the 'golden standard' of an established, small-diameter head conventional type of total hip arthroplasty. This thesis focuses on the results of a randomised clinical trial that comparedring a metal-on-metal resurfacing hip arthroplasty to a metal-on-metal conventional type of total hip arthroplasty. The randomised clinical trial formed the base of

several related studies undertaken to give a better understanding of the adverse reactions that can be encountered related to metal-on-metal bearings and the value and interpretation of metal ion analysis and cross-sectional imaging. For this thesis, seven objectives were formulated, which are further outlined in the next paragraphs.

The objectives of this thesis were to:

1. Determine the effect of preference bias for a specific implant on satisfaction and short-term clinical outcomes.
2. Obtain an objective comparison between the clinical results of a metal-on-metal resurfacing hip arthroplasty and a small-diameter head metal-on-metal total hip arthroplasty at mid-term follow-up.
3. Determine the difference in metal ion release between a resurfacing hip arthroplasty and a small-diameter head total hip arthroplasty.
4. Determine if metal ion concentrations in whole blood and serum can be used interchangeably, and if a formula can give a reliable conversion from serum to whole blood.
5. Define if concerns on metal ion release after metal-on-metal hip arthroplasty can be extrapolated to a metal-on-metal discus arthroplasty in the lumbar spine.
6. Determine if periprosthetic lesions, as seen on Magnetic Resonance Imaging (MRI) scans, and classified as pseudotumours, are exclusively seen around metal-on-metal hip implants.
7. Present a case report of a patient with a destructive pseudotumour in the absence of a metal-on-metal bearing.

Outline of this thesis

Chapter 2: Determination of the effect of preference bias for a specific implant on satisfaction and short-term clinical outcomes.

A randomised trial is an ideal study design to obtain an objective comparison between a new experimental device, such as comparing a resurfacing hip implant, with a golden standard. However, at the time of enrolment of the randomised clinical trial that compared

the resurfacing hip (RHA) implant to a small-diameter head metal-on-metal total hip arthroplasty (MoM THA), the RHA had been considerably promoted. Patients were influenced by the promising stories and preferred to receive a resurfacing implant rather than the golden standard. The high preference for the resurfacing hip implant made it hard to recruit patients for the randomised trial. Since the RHA was considered an experimental device, patients were obliged to participate in intensive follow-up with clinical outcome scores, radiographs and metal ion level. As a compromise, a cohort was created that included patients, who insisted upon having a resurfacing implant and, as a consequence were not able to participate in the randomised comparison trial. The patients included in this cohort were considered to be biased due to their profound preference. It can be supposed that patients with a profound preference are more satisfied postoperative and score better on the subjective clinical scores. For patients included within the randomized trial, this can be questioned. The availability of two groups of patients - with and without a profound preference - enabled a study that compared the satisfaction and clinical results of patients, who insisted on getting a RHA and those who were simply allocated to a RHA by randomisation. Chapter 2 presents an analysis of whether a profound preference for a RHA is a confounding factor or not and if it affects the subjective clinical results and patients' satisfaction in the short-term.

Chapter 3: Obtaining an objective comparison between the clinical results of a metal-on-metal resurfacing hip arthroplasty and a small-diameter head metal-on-metal total hip arthroplasty at mid-term follow-up.

And

Determination of the difference in metal ion release between a resurfacing hip arthroplasty and a small-diameter head total hip arthroplasty.

The RHA was promoted as an implant with a better stability and function that would enable patients to function on a higher activity level. Expectations of patients and their surgeons were high at the time of RHA introduction. However, long-term clinical results that balanced the RHA against a golden standard were lacking. A prospective randomised clinical trial was

initiated to assess the clinical scores, complication rate and survival of the RHA, compared to a MoM THA. Patients were followed with clinical scores, radiographs and metal ion levels in blood were determined at regular time intervals. In Chapter 3, the results of the randomised clinical trial are given at a three to five-year follow-up, including the encountered adverse reactions associated with the MoM bearings implants. In addition, metal ion levels in either the RHA or MoM THA were analysed, and an evolution in time is presented.

Chapter 4: Determining if metal ion concentrations in whole blood and serum can be used interchangeably, and if a formula can give a reliable conversion from serum to whole blood.

Metal ion concentrations in blood rise after patients obtain a metal-on-metal bearing implants, as presented in Chapter 3. Cobalt and chromium ions can be detected in various matrices, such as whole blood and serum and can be used for the evaluation of the metal ion concentrations. The knowledge of their interpretation and a possible superiority of measurements in serum over whole blood are, however, under debate. There is no consensus in literature as to whether serum levels are superior to whole blood levels or vice versa. Furthermore, cut-off points are not specified, and since metal ion levels in serum and whole blood are different, the outcome and interpretation of the cut off points are obscured. Patients, who enrolled in the randomised clinical trial, were evaluated for metal ion concentrations at regular intervals. The results of the prospective follow-up of cobalt and chromium ion levels, in both whole blood and serum, are presented in Chapters 3 and 4. These data could additionally be used to analyse if measurements in serum and whole blood can be used interchangeably (Chapter 4). A conversion formula was generated to calculate whole blood metal ion levels from serum levels and practical guidelines were developed for clinical use in the interpretation of metal ion levels.

Chapter 5: Defining if concerns on metal ion release after metal-on-metal hip arthroplasty can be extrapolated to a metal-on-metal discus arthroplasty in the lumbar spine.

It became clear that metal ion levels in blood rise after implantation of a metal-on-metal hip arthroplasty. Due to this rise of metal ions levels in blood, concerns arose on the systemic and local consequences. Many consequences were and are still uncertain, but the occurrence

of 'adverse reactions to metal ion debris' (ARMD) was one that is related to excessive metal ion release. The term ARMD was used to cover a sequel of adverse events, such as oedema, osteolysis and fluid-filled or solid lesions collections surrounding the hip implants after implantation of a metal-on-metal device. The hazardous side effects gave rise to several guidelines for a close follow-up of metal-on-metal hip arthroplasties to screen for ARMD. By comparison, very little attention has been paid to this phenomenon in other orthopaedic metal-on-metal implants in other joints. For instance, in spinal surgery, a metal-on-metal total disc arthroplasty is used. The question has arisen as to if elevated metal ion levels can also be detected in patients with these metal-on-metal implants. Chapter 5 presents the results of a study, in which the cobalt and chromium ion concentrations in patients with a total disc arthroplasty were evaluated and compared to metal ion levels of patients with a metal-on-metal hip implant.

Chapter 6: Determining if periprosthetic lesions, as seen on MRI, and classified as pseudotumours are exclusively seen around metal-on-metal hip implants.

The various guidelines that were developed for follow-up of patients with a metal-on-metal implant were recommended to screen patients using cross-sectional imaging, such as ultrasound, Computed Tomography (CT) and MRI. As a result, the presence of soft-tissue and fluid collections, muscle atrophy and oedema have been reported in relation to joint arthroplasties in both symptomatic and asymptomatic patients. Most depicted lesions were classified as pseudotumours, a form of ARMD that is used to describe solid and fluid-filled lesions surrounding hip arthroplasties. These pseudotumours have been generally defined as a serious adverse reaction, although the clinical consequence of many of these findings is unknown. Since pseudotumours are also seen in patients without metal-on-metal bearings, it can be hypothesised that identical pseudotumour-like lesions might be present in patients with bearings other than metal-on-metal, and that these lesions are subsequently classified as pseudotumours by current classification systems. Chapter 6 presents the prevalence of periprosthetic lesions diagnosed by metal-artefact-reducing sequence-MRI in three groups of patients: 1) RHA, 2) MoM THA and 3) asymptomatic patients with a small-diameter ceramic-on-polyethylene (CoP) THA. The depicted periprosthetic lesions are graded by three pseudotumour classification systems given in literature.

Chapter 7: A case report of a patient with a destructive pseudotumour in the absence of a metal-on-metal bearing

The mechanism and source of metal ion release is another point of debate. In general, metal ions and particles are generated by wear from the articulating surface, and corrosion. However, ARMD has also been reported in retrieval studies that included patients without excessive wear of the articulating surfaces. The role of other sources, such as the taper-head junction is obscure. In contrast to RHA, a THA uses a taper-head junction. This junction may potentially be a source of metal corrosion product and may trigger ARMD. Chapter 7 presents a case report of a patient with a destructive pseudotumour without a metal-on-metal articulating surface. This case is used to outline the potential sources and risk factors that may have initiated ARMD.

Finally, in Chapter 8, the preceding chapters are summarised and discussed.

REFERENCES

1. Rijksinstituur voor Volksgezondheid en Milieu. Artrose: Hoe vaak komt artrose voor en hoeveel mensen sterven eraan? *Nationaal Kompas Volksgezondheid*. 2011.
2. Wiles P. The surgery of the osteoarthritic hip. *Br J Surg* 1958;45-193:488-97.
3. Hernigou P. Smith-Petersen and early development of hip arthroplasty. *Int Orthop* 2014;38-1:193-8.
4. McKee GK, Watson-Farrar J. Replacement of arthritic hips by the McKee-Farrar prosthesis. *J Bone Joint Surg Br* 1966;48-2:245-59.
5. Ethgen O, Bruyere O, Richy F, Dardennes C, Reginster JY. Health-related quality of life in total hip and total knee arthroplasty. A qualitative and systematic review of the literature. *J Bone Joint Surg Am* 2004;86-A-5:963-74.
6. Rasanen P, Paavolainen P, Sintonen H, Koivisto AM, Blom M, Ryynanen OP, Roine RP. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. *Acta Orthop* 2007;78-1:108-15.
7. No authors listed. Landelijke Registratie Orthopedische Implantaten. LROI-Rapportage 2014: Orthopedische Implantaten in Beeld. 2014.
8. Otten R, van Roermund PM, Picavet HS. [Trends in the number of knee and hip arthroplasties: considerably more knee and hip prostheses due to osteoarthritis in 2030]. *Ned Tijdschr Geneeskd* 2010;154:A1534.
9. Patel A, Pavlou G, Mujica-Mota RE, Toms AD. The epidemiology of revision total knee and hip arthroplasty in England and Wales: a comparative analysis with projections for the United States. A study using the National Joint Registry dataset. *Bone Joint J* 2015;97-B-8:1076-81.
10. Charnley J. Arthroplasty of the hip. A new operation. *Lancet* 1961;1-7187:1129-32.
11. Skytta ET, Jarkko L, Antti E, Huhtala H, Ville R. Increasing incidence of hip arthroplasty for primary osteoarthritis in 30- to 59-year-old patients. *Acta Orthop* 2011;82-1:1-5.
12. Berry DJ, Harmsen WS, Cabanela ME, Morrey BF. Twenty-five-year survivorship of two thousand consecutive primary Charnley total hip replacements: factors affecting survivorship of acetabular and femoral components. *J Bone Joint Surg Am* 2002;84-A-2:171-7.
13. De Kam DC, Busch VJ, Veth RP, Schreurs BW. Total hip arthroplasties in young patients under 50 years: limited evidence for current trends. A descriptive literature review. *Hip Int* 2011;21-5:518-25.

14. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet* 2007;370-9597:1508-19.
15. Smith-Petersen MN. Evolution of mould arthroplasty of the hip joint. *J Bone Joint Surg Br* 1948;30B-1:59-75.
16. Caton J, Prudhon JL. Over 25 years survival after Charnley's total hip arthroplasty. *Int Orthop* 2011;35-2:185-8.
17. Chandler HP, Reineck FT, Wixson RL, McCarthy JC. Total hip replacement in patients younger than thirty years old. A five-year follow-up study. *J Bone Joint Surg Am* 1981;63-9:1426-34.
18. Dorr LD, Takei GK, Conaty JP. Total hip arthroplasties in patients less than forty-five years old. *J Bone Joint Surg Am* 1983;65-4:474-9.
19. Jones LC, Hungerford DS. Cement disease. *Clin Orthop Relat Res* 1987-225:192-206.
20. Maloney WJ, Jasty M, Harris WH, Galante JO, Callaghan JJ. Endosteal erosion in association with stable uncemented femoral components. *J Bone Joint Surg Am* 1990;72-7:1025-34.
21. Willert HG, Semlitsch M. Reactions of the articular capsule to wear products of artificial joint prostheses. *J Biomed Mater Res* 1977;11-2:157-64.
22. Holt G, Murnaghan C, Reilly J, Meek RM. The biology of aseptic osteolysis. *Clin Orthop Relat Res* 2007;460:240-52.
23. Hanna SA, Somerville L, McCalden RW, Naudie DD, MacDonald SJ. Highly cross-linked polyethylene decreases the rate of revision of total hip arthroplasty compared with conventional polyethylene at 13 years' follow-up. *Bone Joint J* 2016;98-B-1:28-32.
24. Lindalen E, Nordsletten L, Hovik O, Rohrl SM. E-vitamin infused highly cross-linked polyethylene: RSA results from a randomised controlled trial using 32 mm and 36 mm ceramic heads. *Hip Int* 2015;25-1:50-5.
25. Triclot P. Metal-on-metal: history, state of the art (2010). *Int Orthop* 2011;35-2:201-6.
26. Zahiri CA, Schmalzried TP, Ebramzadeh E, Szuszczewicz ES, Salib D, Kim C, Amstutz HC. Lessons learned from loosening of the McKee-Farrar metal-on-metal total hip replacement. *J Arthroplasty* 1999;14-3:326-32.
27. McKellop H, Park SH, Chiesa R, Doorn P, Lu B, Normand P, Grigoris P, Amstutz H. In vivo wear of three types of metal on metal hip prostheses during two decades of use. *Clin Orthop Relat Res* 1996-329 Suppl:S128-40.
28. Sieber HP, Rieker CB, Kottig P. Analysis of 118 second-generation metal-on-metal retrieved hip implants. *J Bone Joint Surg Br* 1999;81-1:46-50.

29. McMinn DJ. Development of metal/metal hip resurfacing. *Hip Int* 2003;13-1:41-53.
30. Amstutz HC, Clarke IC, Christie J, Graff-Radford A. Total hip articular replacement by internal eccentric shells: the "tharies" approach to total surface replacement arthroplasty. *Clin Orthop Relat Res* 1977-128:261-84.
31. Amstutz HC, Dorey F, O'Carroll PF. THARIES resurfacing arthroplasty. Evolution and long-term results. *Clin Orthop Relat Res* 1986-213:92-114.
32. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 year: results of 2- to 9-year followup. *Clin Orthop Relat Res* 2007;460:159-64.
33. Daniel J, Pynsent PB, McMinn DJ. Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis. *J Bone Joint Surg Br* 2004;86-2:177-84.
34. Vendittoli PA, Lavigne M, Roy AG, Lusignan D. A prospective randomized clinical trial comparing metal-on-metal total hip arthroplasty and metal-on-metal total hip resurfacing in patients less than 65 years old. *Hip Int* 2006;16 Suppl 4:73-81.
35. Anissian HL, Stark A, Gustafson A, Good V, Clarke IC. Metal-on-metal bearing in hip prosthesis generates 100-fold less wear debris than metal-on-polyethylene. *Acta Orthop Scand* 1999;70-6:578-82.
36. Beaule PE, Schmalzried TP, Udomkiat P, Amstutz HC. Jumbo femoral head for the treatment of recurrent dislocation following total hip replacement. *J Bone Joint Surg Am* 2002;84-A-2:256-63.
37. Burroughs BR, Hallstrom B, Golladay GJ, Hoeffel D, Harris WH. Range of motion and stability in total hip arthroplasty with 28-, 32-, 38-, and 44-mm femoral head sizes. *J Arthroplasty* 2005;20-1:11-9.
38. Padgett DE, Lipman J, Robie B, Nestor BJ. Influence of total hip design on dislocation: a computer model and clinical analysis. *Clin Orthop Relat Res* 2006;447:48-52.
39. Landelijke Registratie Orthopedische Implantaten. LROI Rapportage 2007-2011. 2012.
40. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. *J Bone Joint Surg Am* 2003;85-A-11:2168-73.
41. Grigoris P, Roberts P, Panousis K, Bosch H. The evolution of hip resurfacing arthroplasty. *Orthop Clin North Am* 2005;36-2:125-34, vii.
42. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplasty* 2004;19-8 Suppl 3:78-83.

43. MacDonald SJ. Metal-on-metal total hip arthroplasty: the concerns. *Clin Orthop Relat Res* 2004-429:86-93.

44. Shimmin AJ, Bare J, Back DL. Complications associated with hip resurfacing arthroplasty. *Orthop Clin North Am* 2005;36-2:187-93, ix.

CHAPTER 2

No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty

Pepijn Bisseling, José M H Smolders,
Annemiek Hol, Job L C van Susante

Acta Orthop. 2011 Apr;82(2):161-5.

ABSTRACT

Background and purpose: Hip resurfacing arthroplasty (RHA) is done in patients who often have a high preference for the method. This preference can influence the clinical outcome and satisfaction. We evaluated the potential influence of this preference bias.

Patients and methods: From an ongoing randomized trial comparing RHA with total hip arthroplasty, 28 consecutive patients (28 hips) who had been allocated to an RHA were characterized as the "randomized" group. Twentytwo other patients (24 hips) who had refused participation and had especially requested an RHA were characterized as the "preference" group. Harris hip score (HHS), Oxford hip score (OHS), University of California at Los Angeles activity scale (UCLA), Short Form 12 (SF-12), and visual analog scale satisfaction score (VAS) were assessed in both groups.

Results: Both groups had a high implant satisfaction score (97/100 for the "preference" group and 93/100 for the "randomized" group) at 12 months. The HHS, OHS, and UCLA were similar at baseline and also revealed a similar improvement up to 12 months ($p < 0.001$). Regarding the SF-12, the "preference" group scored lower on the mental subscale preoperatively ($p = 0.03$), and there was a greater increase after 12 months ($p = 0.03$).

Interpretation: We could not show that there was any influence of preference on satisfaction with the implant and early clinical outcome in patients who underwent RHA. The difference in mental subscale scores between groups may still indicate a difference in psychological profile.

INTRODUCTION

The outcome of any surgical treatment is influenced by several factors. Apart from the surgical intervention itself, co-morbidities and postoperative rehabilitation—and also factors such as patients' perception, confidence, and expectations—contribute to the final result and patient satisfaction. Nowadays, most patients have access to the internet and other sources of information, and are well-informed. Their conceptions will lead beliefs and expectations, which will in turn lead to preferences. Preference for a specific treatment can influence the outcome and can introduce bias into assessments of satisfaction and acceptability.[1-6] This might be a confounding factor in a trial, and may affect the validity of the results. To obtain hard evidence of any possible preference effects is problematic, as it is difficult to reliably distinguish between simple therapeutic effects and preference effects mediated through psychological pathways in experiments.[7]

The dilemma of a possible influence of preference is frequently encountered in studies in orthopedic surgery. For example, the interest in resurfacing hip arthroplasty (RHA) has grown in the past 15 years and has received much international attention.[8-10] The results reported regarding the short-term and long-term follow-up of RHA appear to correspond with the results of conventional total hip arthroplasty (THA) and the satisfaction rates reported have been 90–100%.[11-16] Hip resurfacing surgeons generally deal with patients with a profound preference for this particular implant. We have not found any studies that have incorporated the possible influence of preference of the patient for an RHA into their results, and it can be speculated whether these results are influenced by this preference and perception on the part of the patients.

In an ongoing randomized trial comparing RHA with conventional THA, we encountered—as expected—some difficulty in recruiting patients for inclusion, since several patients had a specific demand for RHA. In this way, RHAs were performed in two groups of patients: (1) an unbiased "randomized" group without any preferences, willing to participate in the ongoing trial, and simply allocated to RHA; and (2) a "preference" group of "potentially biased" patients with a specific demand for RHA and who declined participation in the trial. We could therefore evaluate the potential role of preference bias on implant satisfaction and early clinical outcome. We hypothesized that patients in the "preference" group would be more satisfied than the patients in the "randomized" group. On the other hand, patients

with a high degree of preference could have such high expectations of the treatment that they might be difficult to fulfill, which would lead to lower satisfaction compared to patients without any preference.

PATIENTS AND METHODS

From April 2007 through March 2010, patients under 65 years with primary arthritis of the hip were evaluated for eligibility to enter the randomized controlled trial (RCT) comparing RHA with THA. After having given informed consent, patients with a strong preference for RHA (and who were therefore unwilling to be randomized) entered the prospective cohort study—the "preference" group. Patients with no preference were enrolled in the RCT to receive either an RHA or a THA. The current study included all patients in the "preference" group and all patients in the RCT who were allocated to RHA, with a minimum follow-up of 6 months.

The criteria for inclusion in both the RCT and the cohort were identical: patients between 35 and 65 years old, eligible for primary hip replacement because of osteoarthritis, congenital hip dysplasia, or posttraumatic arthritis. Patients were excluded in case of (previous) infection of the hip, hip fracture, avascular necrosis with collapse, osteoporotic bone mineral density index levels of the involved hip (t-score < 2.5), renal failure, or hip revision of the primary index procedure.

All patients received a Conserve Plus RHA (Wright Medical Technology, Arlington, TN). The operations were performed through a standard posterolateral approach by a senior hip surgeon with considerable experience in RHA implants.[17] Both groups received identical antibiotic prophylaxis, periarticular ossification prophylaxis, and thrombosis prophylaxis during hospital admission, and six weeks afterwards. The patients had identical rehabilitation protocols with unrestricted weight bearing according to individual tolerance, starting on the first postoperative day.

Fifty patients were included in the study, with 28 implants (28 patients) in the "randomized" group and 24 implants (22 patients) in the "preference" group (Figure 1 and Table I). All patients in the "preference" group and 22 of the 28 patients in the "randomized" group completed the follow-up term of 12 months. The remaining six patients had a follow-

up of 6 months. All patients completed a questionnaire that included the Short Form 12 (SF-12) and Oxford hip score (OHS) preoperatively, at 6 months, and at 12 months. The Harris hip score (HHS) and the University of California at Los Angeles activity scale (UCLA) were assessed by an independent member of the research staff (AH) who collected and registered all the forms. Satisfaction with the implant was measured on a numeric scale (visual analog scale satisfaction score (VAS)) of 0–100 mm, where 100 mm corresponded to being completely satisfied.

Approval for the randomized clinical trial and the cohort follow-up was obtained from the regional ethics committee of the Radboud University Nijmegen Medical Centre, with issue number LTC 419-071206 and date of approval 01/02/2007. All patients agreed to sign an informed consent document. The EudraCT number asigned to the randomized controlled trial was 2006-005610-12.

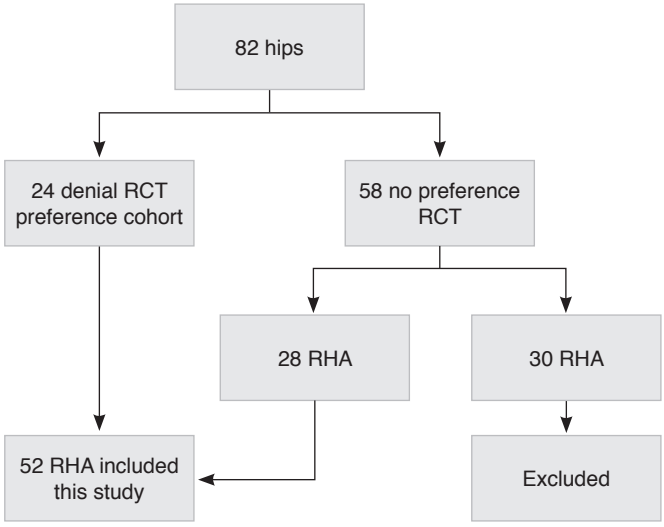


Figure 1. Recruitment of patients to the study

Table I. Demographics of patients

	"Preference" group (n = 24)	"Randomized" group (n = 28)	p-value
Age			
median	52	58	
interquartile range	48–56	52–62	0.01
Sex: Male	15	13	0.2
Diagnosis			
Osteoarthritis	24	26	
Hip dysplasia	–	1	
Avascular necrosis	–	1	0.5

Statistics

Variables were checked for normal distribution with the Shapiro-Wilk test. A value of < 0.05 was defined as the absence of a normal distribution. The mean and standard deviation (SD) were used for normally distributed variables and the median and interquartile range (IQR) for variables without normal distribution. Differences between the groups were determined by the Student's t-test for variables with normal distribution, the Mann-Whitney test for variables without normal distribution, and the Pearson Chi-square test for categorical variables (sex and diagnosis). Variables that were not normally distributed were: age, blood loss, the preoperative OHS and UCLA scores, the VAS satisfaction score at 12 months, and the change in satisfaction score between 6 and 12 months. These p-values are marked with the superscript β. Significance was defined as p-values of < 0.05. SPSS software version 15.0 was used for statistical analysis.

RESULTS

The characteristics of the patients are given in Table I. Both groups were similar regarding sex and diagnosis, but the patients in the "preference" group were younger than in the "randomized" group. Mean operation time ("preference" group: 81 min (SD 15); "randomized" group: 76 min (SD 11); $p = 0.2$) and median blood loss ("preference" group: 300 (288–313) mL; "randomized" group: 300 (200–300) mL; $p = 0.4^{\beta}$) were similar in both groups. Similar implants sizes were used in both groups ($p = 0.7$).

The preoperative HHS, OHS, and UCLA scores were similar in both groups (Figure 2). The SF-12 score, however, was higher (88 (SD 14)), in the "randomized" group than in the "preference" group (80 (SD 12)) ($p = 0.03$). This difference mainly originated from inter-group differences in the mental subscale. A mean score of 47 (SD 13) on the mental subscale was found in the "preference" group, as opposed to 53 (SD 10) in the "randomized" group ($p = 0.05$).

The HHS, OHS, and UCLA scores all showed a postoperative improvement at 12 months compared to the preoperative baseline scores for both groups ($p < 0.001$) (Figure 2). These improvements were similar between the groups ($p = 0.8$, $p = 0.7$, and $p = 0.4$, respectively). For the SF-12, however, at 12 months a better recovery was achieved from preoperative levels in the "preference" group than in the "randomized" group ($p = 0.03$).

Patient satisfaction (VAS) was assessed at 6 and 12 months for both groups. Both groups had a high satisfaction score, with a median of 97 for the "preference" group and 93 for the "randomized" group at the 12-month follow-up ($p = 0.7^{\beta}$). Similar scores were obtained at the 6-month follow-up.

Two complications occurred in the "preference" group. One patient had a perioperative collum fissure with a delayed, but uneventful, recovery—and with clinical and satisfaction scores that matched within the interquartile range. Another patient had complaints of possible anterior impingement of the RHA. This patient had clinical and satisfaction scores that dropped below the interquartile range. With exclusion of both patients, the median satisfaction score remained at 97 for the "preference" group and 93 for the "randomized" group ($p = 0.6^{\beta}$). With this exclusion, there were minimal changes in clinical scores, but with no consequences for the differences between the "preference" group and the "randomized" group ($p = 1.0$, $p = 0.9$, $p = 0.3$, and $p = 0.01$ for HHS, OHS, UCLA, and SF-12, respectively). The other 50 RHAs all had an uneventful clinical course.

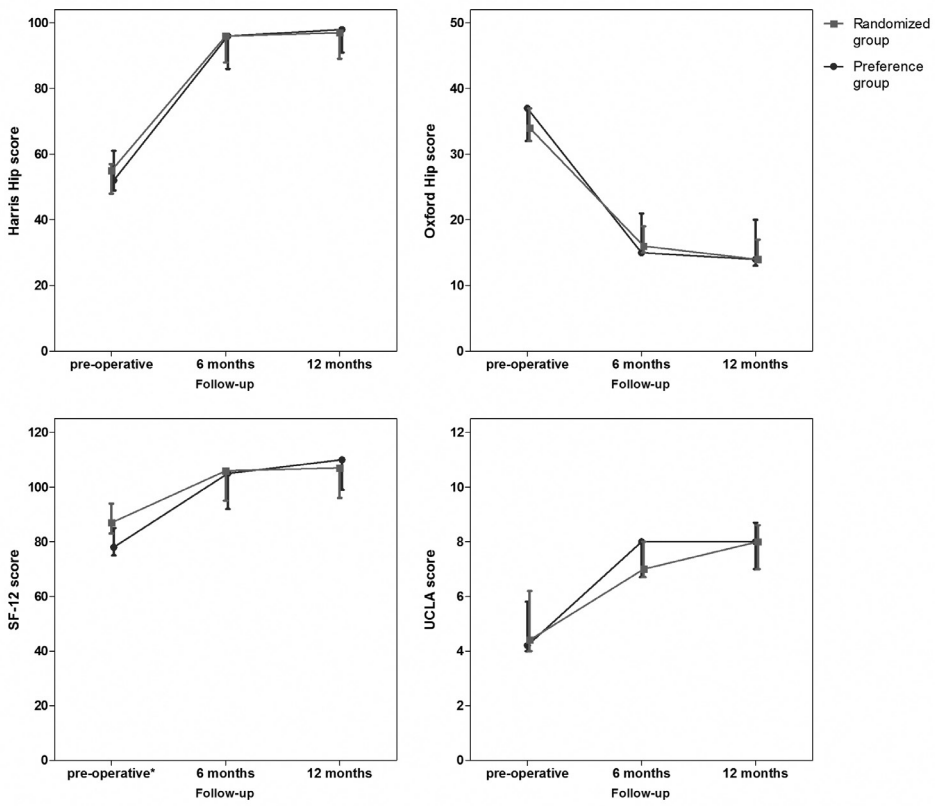


Figure 2. Clinical scores (HHS, Oxford, SF-12 and UCLA) with 95%-confidence interval preoperatively, at 6 and 12 months.

* In the horizontal axis of the SF-12 score represents a significant difference at baseline preoperative scores ($p<0.05$).

DISCUSSION

In this prospective comparative study, patient satisfaction and early clinical outcome in "biased" patients with a high preference for resurfacing hip arthroplasty (the "preference" group) did not differ statistically significantly from the results in unbiased patients who were simply allocated to an RHA after randomization in a separate randomized controlled trial (the "randomized" group). There was, however, a trend toward better satisfaction in the "preference" group. Only for the preoperative SF-12 values, and for the mental subscale in particular, was any statistically significant difference between groups encountered, in favor of the "randomized" group.

In spite of the fact that the potential bias from treatment preferences is a well-recognized phenomenon in orthopedic practice, there have only been a few studies dealing with this clinical dilemma. Van der Windt et al. (2000), for example, demonstrated a success rate of 85% in patients with shoulder pain who received their preferred therapy compared to a 64% success for those who underwent the same treatment against their preference.[6] In another study, any direct influence of preference for a certain therapy on shoulder pain could not be confirmed; however, the authors revealed that in general patients with a preference before randomization tended to have a better overall outcome than those with no preference.[4]

Randomized controlled trials are usually regarded as the gold standard in comparing two therapeutic treatments, as they diminish possible confounding factors. To study the potential influence of preference bias on the outcome of one and the same surgical procedure, randomization is, however, not a feasible tool for obvious reasons. Our randomized controlled trial on THA and RHA confirmed for us the existence of patient preference for RHA; it was difficult to recruit patients for the trial. Many patients had a preference for RHA even after being informed about the absence of any evidence in the literature of a benefit of RHA over a conventional THA.[14,18] The presence of a cohort of patients with a clear preference for RHA and a group of patients allocated to RHA after randomization enabled us to gain some insight into the possible role of preference bias.

Our study had some limitations, however. The number of patients in both groups was small, eventually resulting in a power of 59% to detect a clinical significant difference of 10 on the VAS for patient satisfaction in a post hoc power analysis. A power of 80% was calculated to detect a difference of 13 on the VAS for patient satisfaction. Clearly, there was

a small difference in outcome between the groups and a larger number of patients may eventually have revealed a statistically significant difference in patient satisfaction between the groups. On the other hand, the power in our study was substantial enough for us to question whether such a difference would have been of clinical importance.

Another limitation of our study may have been the short follow-up. However, evaluated the Birmingham hip arthroplasty in a five to eight year follow-up and demonstrated that the satisfaction rate did not change substantially after the first postoperative year.[12] Lingard et al. also showed a ceiling effect after one year.[13] In addition, it is debatable whether a potential difference in satisfaction after one year would be influenced by preference, because expectations would be most manifest in the short period after the operation.

Two patients with a bilateral prosthesis were included. One must assume that the outcome of two prostheses in the one patient cannot be interpreted independently. The result of the first prosthesis can either positively or negatively influence the outcome of the second, and vice versa.[19] Study outcome in general may be biased by this phenomenon; however, the number of bilateral prostheses in our study was low and exclusion of the two patients with bilateral prostheses did not have any consequences for our findings (data not shown).

Apart from the presence or absence of a profound preference for an RHA, both groups matched regarding most demographic features and preoperative functional scores. The size of the femoral component of the implant was similar in both groups. This is important, as component size is known to influence the outcome of RHA.[20,21]

The only differences between the groups were age and preoperative SF-12 score. The difference in age between the groups suggests that younger patients are less willing to participate in a randomized clinical trial. As for the SF-12, and for the mental subscale in particular, patients in the “preference” group had a lower preoperative score. There were no outliers that could explain this difference between the groups. One could argue whether there is reason to believe that patients with a high preference for a certain treatment generally have a different psychological profile than patients who are willing to participate in a randomized trial. This finding has been recognized before.[3]

In conclusion, we could not demonstrate any influence of preference on implant satisfaction and early clinical outcome in patients with an RHA. A trend towards a relatively higher degree of satisfaction was nevertheless established for patients with a specific request for RHA. The significant difference in mental subscale scores encountered between groups may indicate a difference in psychological profile.

REFERENCES

1. Klaber Moffett JA, Jackson DA, Richmond S, Hahn S, Coulton S, Farrin A, Manca A, Torgerson DJ. Randomised trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: outcomes and patients' preference. *Bmj* 2005;330-7482:75.
2. McPherson K, Britton A. Preferences and understanding their effects on health. *Qual Health Care* 2001;10 Suppl 1:i61-6.
3. McPherson K, Britton AR, Wennberg JE. Are randomized controlled trials controlled? Patient preferences and unblind trials. *J R Soc Med* 1997;90-12:652-6.
4. Thomas E, Croft PR, Paterson SM, Dziedzic K, Hay EM. What influences participants' treatment preference and can it influence outcome? Results from a primary care-based randomised trial for shoulder pain. *Br J Gen Pract* 2004;54-499:93-6.
5. Torgerson DJ, Klaber-Moffett J, Russell IT. Patient preferences in randomised trials: threat or opportunity? *J Health Serv Res Policy* 1996;1-4:194-7.
6. van der Windt DA, Koes BW, van Aarst M, Heemskerk MA, Bouter LM. Practical aspects of conducting a pragmatic randomised trial in primary care: patient recruitment and outcome assessment. *Br J Gen Pract* 2000;50-454:371-4.
7. McPherson K, Chalmers I. Incorporating patient preferences into clinical trials. Information about patients' preference must be obtained first. *Bmj* 1998;317-7150:78; author reply -9.
8. Chen S MM, Estabrooks T, Amuah J E, Zhu N. Hip Resurfacing Arthroplasty: Findings From the Canadian Joint Replacement Registry. Canadian Institute for Health Information, Toronto, Canada 2007.
9. No authors listed. National Joint Registry for England and Wales. 1st Annual report. Hemstead, England: The National Joint Registry (NJR) Centre 2004.
10. No authors listed. National Joint Registry for England and Wales. 6th Annual report 2009. Hemstead, England: The National Joint Registry (NJR) Centre 2009:48.
11. Amstutz HC, Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA for patients younger than 50 year: results of 2- to 9-year followup. *Clin Orthop Relat Res* 2007;460:159-64.
12. Khan M, Kuiper JH, Edwards D, Robinson E, Richardson JB. Birmingham hip arthroplasty: five to eight years of prospective multicenter results. *J Arthroplasty* 2009;24-7:1044-50.
13. Lingard EA, Muthumayandi K, Holland JP. Comparison of patient-reported outcomes between hip resurfacing and total hip replacement. *J Bone Joint Surg Br* 2009;91-12:1550-4.

14. Mont MA, Marker DR, Smith JM, Ulrich SD, McGrath MS. Resurfacing is comparable to total hip arthroplasty at short-term follow-up. *Clin Orthop Relat Res* 2009;467-1:66-71.
15. Pollard TC, Baker RP, Eastaugh-Waring SJ, Bannister GC. Treatment of the young active patient with osteoarthritis of the hip. A five- to seven-year comparison of hybrid total hip arthroplasty and metal-on-metal resurfacing. *J Bone Joint Surg Br.* Vol. 88, 2006:592-600.
16. Vail TP, Mina CA, Yergler JD, Pietrobon R. Metal-on-metal hip resurfacing compares favorably with THA at 2 years followup. *Clin Orthop Relat Res* 2006;453:123-31.
17. Witjes S, Smolders JM, Beaule PE, Pasker P, Van Susante JL. Learning from the learning curve in total hip resurfacing: a radiographic analysis. *Arch Orthop Trauma Surg* 2009;129-10:1293-9.
18. Lavigne M, Therrien M, Nantel J, Roy A, Prince F, Vendittoli PA. The John Charnley Award: The functional outcome of hip resurfacing and large-head THA is the same: a randomized, double-blind study. *Clin Orthop Relat Res* 2010;468-2:326-36.
19. Bryant D, Havey TC, Roberts R, Guyatt G. How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. *J Bone Joint Surg Am* 2006;88-1:41-5.
20. Crowninshield RD, Maloney WJ, Wentz DH, Humphrey SM, Blanchard CR. Biomechanics of large femoral heads: what they do and don't do. *Clin Orthop Relat Res* 2004-429:102-7.
21. Prosser GH, Yates PJ, Wood DJ, Graves SE, de Steiger RN, Miller LN. Outcome of primary resurfacing hip replacement: evaluation of risk factors for early revision. *Acta Orthop* 2010;81-1:66-71.

Chen S MM, Estabrooks T, Amua
the Canadian Joint Replacement Registry:
Canada 2007.
9. No authors listed. National Joint Registry for England
England: The National Joint Registry (NJR) Centre 2004.
No authors listed. National Joint Registry for England a
tead, England: The National Joint Registry (NJR) Centr
11. Amst Ball ST, Le Duff MJ, Dorey FJ. Resurfacing THA
results of 2- ear followup. *Clin Orthop Relat Res* 2007;
12. Khan M, Kuiper J rds D, Robinson E, Richardson JB. B
to eight years of prospe ulticenter results. *J Arthroplast*
Lingard EA, Muthumayandi K, nd JP. Comparison of pa
hip resurfacing and total hip replac *J Bone Joint Surg*

CHAPTER 3

Metal ion levels and functional results following resurfacing hip arthroplasty versus conventional small-diameter metal-on-metal total hip arthroplasty; a 3 to 5 year follow-up of a randomized controlled trial

Pepijn Bisseling, José M.H. Smolders,
Annemiek Hol, Job L.C. van Susante

J Arthroplasty. 2015 Jan;30(1):61-7.

ABSTRACT

We present an update of a randomized controlled trial on 71 patients (<65 years) who received either a resurfacing hip arthroplasty (RHA) (n = 38) or cementless 28-mm metal-on-metal (MoM) total hip arthroplasty (THA) (n = 33). Metal ion levels and functional outcome scores were analyzed with a mean follow-up of 58 months (SD 8.1). No clear shifts in relatively good outcome was encountered between RHA and THA. Metal ion levels appear to equalize between groups after 3 years. Median cobalt and chromium remained below 1.3 µg/L throughout follow-up in both groups. Six revisions were performed, of which three for pseudotumour formation (one THA, two RHA). In conclusion there were no clinical differences between the two groups and metal ion levels were lower than other series remained low, however, pseudotumour formation was not eliminated.

INTRODUCTION

The resurfacing hip arthroplasty (RHA) has been marketed as the latest advancement in hip arthroplasty and was targeted at young active patients who needed a hip that would last a lifetime. Based on all (theoretical) advantages RHA and metal-on-metal (MoM) bearings were appealing concepts to both surgeon and patients.[1-8] The potential disadvantages, however, like the more technical demanding procedure, the subsequent potential risk of femoral neck fractures, the occurrence of excessive metal ion release and the adverse reactions to metal debris (ARMD) were less widely specified and in hind view may have been underestimated.[2,9-12] In the rapidly emerging market of RHA, we felt that there was a lack of literature where this new concept was balanced against the 'gold standard' of conventional total hip arthroplasty (THA). In a period with considerable promotion for the use of these MoM implants we undertook a randomized clinical trial to assess the proposed benefits of RHA compared to an established THA (with a small-diameter MoM bearing). On the short term, up to 2 years, we found that all functional outcome scores improved highly significant for both groups.[13] RHA patients scored significantly higher on UCLA, OHS and VAS satisfaction at some intervals, however, it may be argued whether these encountered differences were clinically relevant. Chromium and cobalt blood levels were significantly higher for RHA during the running in phase of 1 year with a tendency towards decreasing levels up to 2 years follow-up. No pseudotumours were encountered in either group at the earlier short-term follow-up report. One RHA was revised for early aseptic loosening and in two THA's a cup insert was exchanged for recurrent dislocation.[13]

In this RCT we questioned whether the functional results of RHA would indeed be superior to a conventional metal bearing THA and whether a large diameter RHA bearing would induce more metal ion release than a relatively small 28-mm diameter similar bearing in a conventional THA. Since there is an ongoing international debate on the surplus value of RHA against conventional THA we felt it appropriate to provide an update of a previous report [13] with now 3 to 5 year follow-up of a randomized trial comparing RHA with a small diameter metal-on-metal THA.

PATIENTS AND METHODS

Study Design and Randomization Procedure

In the original exploratory study[13] patients with osteoarthritis of the hip were randomized to receive either a resurfacing total hip arthroplasty (RHA) or a conventional uncemented small diameter MoM total hip arthroplasty (THA). The study is designed to compare the functional results and metal ion blood levels of patients after RHA versus THA at (the now presented) short and medium follow-up, and eventually the long-term interval.

From June 2007 until January 2010 eighty-two patients were randomly assigned to receive one of two hip implants (RHA versus THA). A computer-generated variable block schedule was used for randomization. An independent statistician generated the randomization list and the resulting treatment allocations were stored in sealed opaque envelopes. Randomization occurred at the outpatient consultation by the orthopaedic surgeon at the time of planning a hip arthroplasty. Patient and the surgeon could not be blinded for the eventual type of implant; neither could, however, influence the randomization outcome. The criteria for inclusion were patients under 65 years, who needed a primary hip arthroplasty for hip arthritis. Patients were excluded if they had (previous) infection of the hip or other sites, hip fracture, avascular necrosis with collapse, osteoporotic bone mineral density, neoplasm, or renal failure. Inclusion and subsequent follow-up of patients are summarized in the consort statement (Figure 1). A per-protocol was used in this study, because revised patients could be followed for metal ions. Two patients were lost to follow-up because of lack of motivation, one in each group (RHA after 12 months, THA after 24 months). Two patients deceased in the THA group, of conditions not related to the implantation of the THA. Ten patients also had a metal-on-metal implant on the contralateral side and thus their metal ion blood levels were evaluated separately. The revision cases are described in detail in the results section. Approval from the regional ethics committee from the Radboud University Nijmegen Medical Centre was obtained, with issue number LTC 419–071206, Committee Human Research number (CCMO) 2007/015 and date of approval 01/02/2007. All patients agreed to sign an informed consent. This study was performed in compliance with the Helsinki declaration. The EudraCT trial register number consigned to this study was 2006-005610-12.

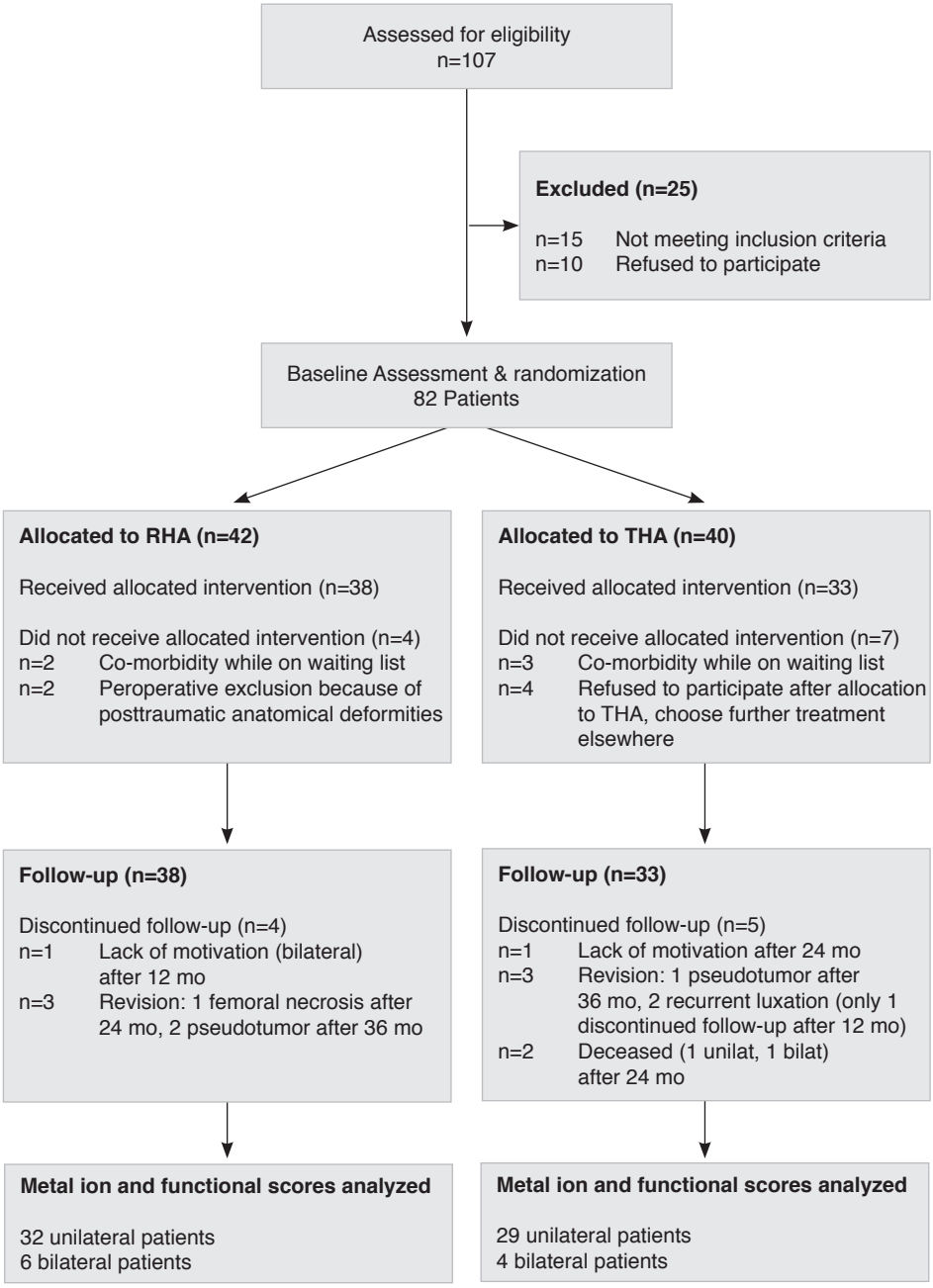


Figure 1. Consort statement

Surgical Technique

The surgical technique, after-treatment and rehabilitation protocol have been described inthe previous report on this study.[13] In the RHA group a resurfacing prosthesis was implanted with both components made of a cast, heat-treated solution-annealed Co–Cr alloy (Conserve plus; Wright Medical Technology, Arlington, Tennessee, USA). In the THA group, an uncemented tapered stem and threaded titanium cup with a polyethylene insert with a metal liner were placed (Zweymuller Classic) together with a metal 28-mm head (Metasul) (Zimmer Orthopaedics, Warsaw, Indiana, USA).

Clinical Evaluation

Questionnaires that included the SF-12, Oxford Hip Score (OHS) and VAS implant satisfaction were taken pre-operatively and at 6, 12, 24, 36 and 60 months. An independent (not blinded) research staff member (AH) assessed the Harris Hip Score (HHS) and the University of California at Los Angeles (UCLA) Activity Score.

Cup inclination was measured on standardized postoperative anterior–posterior (AP) pelvic radiographs.

Cobalt and Chromium Blood Levels

Whole blood samples were collected pre-operatively and at 3, 6, 12, 24, 36 and 60 months post-operatively and assessed on cobalt and chromium concentrations. Blood samples were collected in metal-free vacutainers, the first 5 mL blood was discarded to eliminate any form of metal contamination from the needle. Tubes were stored at 2–8 °C and sent to the laboratory of Toxicology of the University Hospital Ghent (Belgium) for analysis. The metal ion levels were determined using an inductively-coupled plasma mass spectrometer (ICP-MS) on a Perkin Elmer Elan DRC-e, equipped with a standard cross-flow nebulizer and a Dynamic Reaction Cell (Perkin Elmer SCIEX, Canada). Since ten patients with a bilateral metal-on-metal implant had a double exposure to wear and thus tend to have higher metal ion blood levels, these data are presented separately from unilateral implants. Extracted data from the unilateral group were considered to represent the metal ion concentration curves after RHA versus THA most reliably. Following the recommendations of Daniel et al we only report on metal ion levels in whole blood.[14]

Statistical Analysis

Metal ion data distributions were asymmetric and are expressed as a group median with 95% confidence interval, Friedman's ANOVA, was used for analysis. To determine the between-time differences within the groups the non-parametric Wilcoxon signed-rank test was performed, to protect for a type-1 error a Bonferroni correction was applied. To determine differences between the two groups and between functional results the Mann–Whitney U test was used. Symmetrical data are represented by a mean and standard deviation (SD), the tests used for significance are expressed in the legend of Table I. In the boxplots the outliers are represented by a dot (•), extreme outliers (more than three times deviation of the interquartile range from the upper quartile) are characterized by an asterisk (*). Differences were considered statistically significant at $P < 0.05$. Lacking information about metal ion levels and functional results in a randomized setting after a discontinued intervention in some cases, the small number of patients and multiple endpoints make this anexploratory trial. The results should therefore be read as hypotheses. Because of the exploratory character of the study, formal adjustment for multiplicity between endpoints was not made.All statistical analyses were performed using SPSS software (Version 21.0, SPSS Inc. Chicago, IL).

Table I. Patient Characteristics of the Study Population.

	RHA (n = 38)		THA (n = 33)		P-Value
Median age in years (IQR)	57.5	(50–61)	59.2	(51–61)	0.407[a]
Mean body mass index (SD)	26.1	(3.1)	28.0	(5.1)	0.069[b]
Gender (men/women)	21/17		21/12		0.629[c]
Uni- or bilateral MoM prosthesis	32/6		29/4		0.633[c]
Diagnosis (OA/AVN/CHD)[d]	35/1/2		31/0/2		0.785[e]
Charnley category (A/B)	24/14		23/10		0.649[c]
Mean operating time in min(SD)	77.3	(11.2)	55.6	(11.8)	<0.001[b]
Median blood loss in mL (IQR)	300	(100–300)	250	(100–300)	0.993[a]
Cup inclination (range)	45	(30.2-61.6)	48	(31.0-62.3)	0.360[b]

[a] Mann–Whitney U test.

[b] Student's t-test.

[c] Fisher's exact probability test.

[d] OA, osteoarthritis; AVN, avascular necrosis; CHD, congenital hip dysplasia.

[e] Kruskall–Wallis test.

RESULTS

Patient characteristics are described in Table I. Mean follow-up was 58 months (SD 8.1). Mean RHA femoral head size was 48.7 mm (SD 3.5). All patients (excluding revised, LTFU and deceased patients) reached the 36 month follow-up point, and approximately 50% of the patient had their 5-year follow-up available; available number of patients at each time interval is indicated in Table II.

Table II. Clinical Scores and VAS Satisfaction.

		HHS		UCLA Activity		SF-12		OHS		VAS Satisfaction	
RHA											
Preoperative	(n = 38)	57	54–60	5[a]	4–7	88.2[a]	85–94	34	30–36		
6 months	(n = 38)	96[a]	93–98	7[a]	7–8	107.4	99–110	16[a]	14–18	89	82–98
12 months	(n = 38)	98	96–100	8[a]	7–9	107.0	101–110	13	12–16	92[a]	88–96
24 months	(n = 37)	98	96–100	7	7–8	107.5	103–112	13[a]	12–14	94[a]	88–98
36 months	(n = 36)	98	98–100	7	7–8	108.8	100–112	13[a]	12–15	92	85–98
60 months	(n = 14)	96	93–98	7	6–7	108.7	89–116	14	13–17	83	66–99
THA											
Preoperative	(n = 33)	53	44–59	4[a]	4–4	79.8[a]	74–83	37	34–38		
6 months	(n = 33)	93[a]	85–94	7[a]	5–7	100.6	85–110	18[a]	16–23	81.5	75–93
12 months	(n = 33)	96	91–98	7[a]	6–7	106.0	80–110	15	14–17	86[a]	79–91
24 months	(n = 33)	96	93–100	7	6–8	107.7	99–112	15[a]	14–18	88[a]	78–92
36 months	(n = 30)	96	95–100	7	6–8	103.3	99–110	15[a]	13–17	87.5	80–94
60 months	(n = 12)	98	72–100	6	4–10	100.0	85–116	14	12–16	94	79–100

All values are given as the median (95% CI).

a Significant difference between RHA and THA ($P \leq 0.05$).

Clinical Evaluation

The clinical scores are summarized in Table II and Figure 2. In spite of the fact that we performed a randomized trial the preoperative values of UCLA activity score and SF-12 appeared to be significantly lower in the THA group ($P = 0.042$, $r = -0.24$ and $P = 0.007$, $r = -0.32$ respectively). The HHS, OHS, UCLA activity score and SF-12 all improved significantly after surgery for both groups ($P < 0.001$).This improvement in clinical scores remained stable throughout the available follow-up. At 6, 24 and 36 months a significantly better OHS for the RHA patients was found ($P = 0.023$, $r = -0.27$; $P = 0.023$, $r = -0.27$; $P = 0.033$, $r = -0.26$) as compared to THA patients. The HHS at 6 months was higher for the RHA patients ($P = 0.021$, $r = -0.27$).

The median UCLA activity score was significantly better for the RHA patients at 6 and 12 months with medium effect size ($P = 0.10$, $r = -0.30$; $P = 0.002$, $r = -0.37$). RHA patients were significantly more satisfied after 12 months ($P = 0.025$, $r = -0.27$) and 24 months ($P = 0.019$, $r = -0.28$) compared to THA patients, this significant difference disappeared at 36 months. Acetabular component positioning, calculated as the mean cup inclination, did not differ between both groups: RHA 45° (range; 30.2–61.6) and in the THA 48° (range; 31.0–62.3)($P = 0.36$).

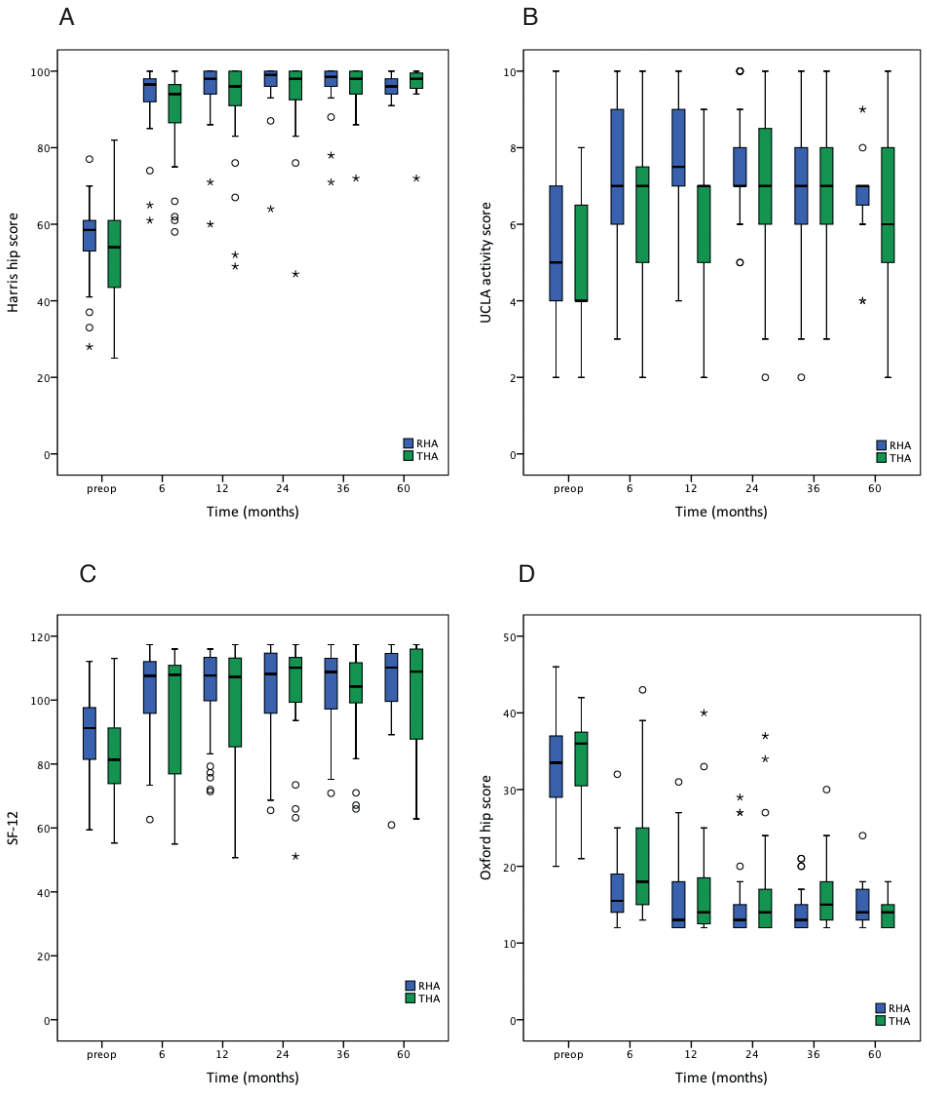


Figure 2.
(A) Boxplot HHS.
(B) Boxplot UCLA activity score.
(C) Boxplot SF-12.
(D) Boxplot OHS.

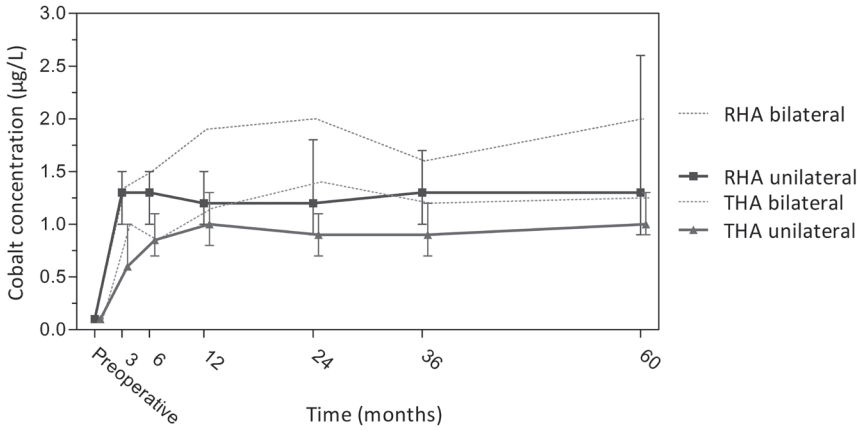
Cobalt and Chromium Blood Levels

The concentrations of chromium and cobalt in whole blood for RHA versus THA for each time interval are summarized in Table III and Figure 3. Baseline preoperative chromium and cobalt concentrations were, as expected, below the reference level of 1.0 µg/L for both groups with a unilateral implant (Mayo Medical Laboratories 2010). Cobalt and chromium blood levels increased significantly ($P < 0.001$) for both RHA and THA after surgery until 6 months postoperatively, with stabilizing concentrations thereafter. Cobalt concentrations were significantly higher for RHA compared to THA at 3 ($P < 0.001$, $r = -0.50$), 6 ($P = 0.006$, $r = -0.35$), 24 ($P = 0.009$, $r = -0.34$) and 36 months ($P = 0.019$, $r = -0.31$).

At 12 and 60 months the difference was no longer significant ($P = 0.148$, $P = 0.126$), however since the median cobalt level did not really change this absence of significant difference may well be explained by the incomplete 5 year follow-up data. Chromium concentrations were also significantly higher for the RHA group, however this time at all postoperative time intervals until 60 months (3 months $P < 0.001$, $r = -0.57$; 6 months $P < 0.001$, $r = -0.47$; 12 months $P < 0.001$, $r = -0.54$; 24 months $P < 0.001$, $r = -0.52$; 36 months $P = 0.012$, $r = -0.33$; 60 months $P = 0.036$, $r = -0.46$).

Cobalt and chromium levels were higher in the subgroup of bilateral MoM implants, yet, did not reveal significantly higher metal ion concentrations as compared to the unilateral group. However, it has to be noted that the bilateral subgroup is small (Table III).

A



B

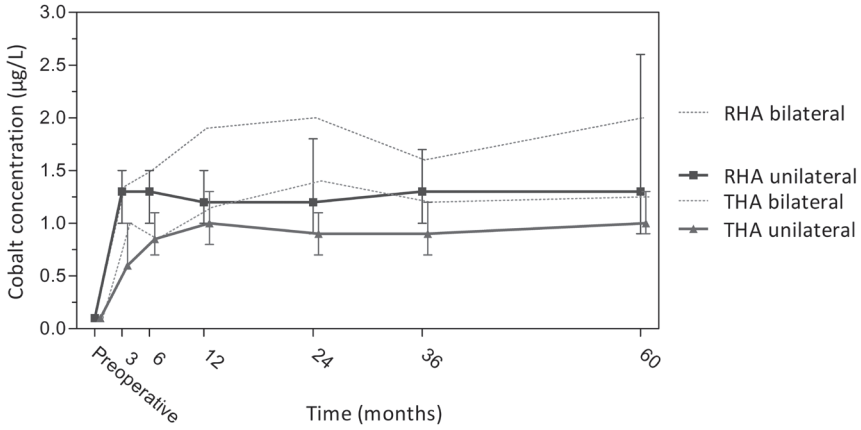


Figure 3.
(A) Errorplot of cobalt concentrations with median (95% CI) in µg/L for RHA (blue) and THA (green) for each time interval.
(B) Errorplot of chromium concentrations with median (95% CI) in µg/L for RHA (blue) and THA (green) for each time interval.

Table III. Cobalt and Chromium Whole Blood Concentrations.

	Preoperative		6 Months		12 Months		24 Months		36 Months		60 Months	
	RHA	THA	RHA	THA	RHA	THA	RHA	THA	RHA	THA	RHA	THA
Unilateral implants												
	(n = 32)	(n = 29)	(n = 32)	(n = 29)	(n = 32)	(n = 29)	(n = 31)	(n = 28)	(n = 31)	(n = 26)	(n = 11)	(n = 9)
Co	0.1	0.1	1.3[a]	0.85[a]	1.2	1.0	1.2[a]	0.9[a]	1.3[a]	0.9[a]	1.3	1.0
	0.1–0.1	0.1–0.1	1.0–1.5	0.7–1.1	1.0–1.5	0.8–1.3	0.9–1.8	0.7–1.1	1.0–1.7	0.7–1.2	0.9–2.6	0.9–1.3
Cr	0.1	0.1	1.1[a]	0.1[a]	1.0[a]	0.5[a]	1.2[a]	0.5[a]	0.9[a]	0.1[a]	0.6[a]	0.1[a]
	0.1–0.1	0.1–0.1	0.8–1.4	0.1–0.6	0.9–1.4	0.1–0.7	0.8–1.8	0.1–0.9	0.5–1.4	0.1–0.7	0.1–1.6	0.1–0.1
Bilateral implants												
	(n = 6)	(n = 4)	(n = 6)	(n = 4)	(n = 6)	(n = 4)	(n = 6)	(n = 4)	(n = 5)	(n = 2)	(n = 3)	(n = 2)
Co	0.2	0.1	1.5	0.85	1.9	1.15	2.0	1.4	1.6	1.2	2.0	1.25
	0.1–1.1	0.1–1.8	1.0–7.9	0.5–2.2	0.9–10.6	0.8–1.3	0.7–6.0	0.7–1.8	0.7–4.9	0.7–1.7	0.8–5.5	0.9–1.6
Cr	0.50	0.1	1.4	0.25	1.6	0.5	1.5	0.8	1.7	0.4	1.0	0.3
	0.1–1.2	0.1–0.8	0.6–3.8	0.1–1.5	0.1–4.9	0.1–0.8	0.1–2.3	0.6–0.8	0.1–2.8	0.1–0.7	0.1–2.0	0.1–0.5

The values (µg/L) are given as the median (95% CI).

[a] Significant difference between RHA and THA ($P \leq 0.05$).

Complications and Revisions

In the conventional THA group three patients with a recurrent dislocation were encountered for which two patients had an early reintervention with cup insert and head exchange, which solved the problem. Follow-up was discontinued in one after 12 months and the other continued the follow-up because of a Metasul inlay. Metal ion levels 1 year after revision stayed below the median cobalt and chromium levels for this group, excluding profound bias on the results from the introduction of a potential new running-in phase in this patient. Another revision in the MoM THA group occurred at 36 months for unclassified pain, which appeared to come from a profound pseudotumour on MRI with the typical aspect of an adverse reaction to metal debris (ARMD) during revision surgery .[15] Whole blood metal ion concentrations in this female patient were relatively low at 36 months (chromium 0.9 µg/L, cobalt 1.0 µg/L). As for the RHA group, three revisions were also encountered. One revision at 24 months, an early aseptic loosening from avascular necrosis of the femoral head mandated a conversion to an intramedullary stem with a large femoral head. The original acetabular component and thus the MoM bearing was maintained since the patient had been pain free for 2 years and cobalt whole blood levels were 2.3 µg/L prior to revision. Two other revisions in female patients occurred after 36 months because of pseudotumour formation on MRI and confirmed during surgery, one with relatively low metal ions at 36 months (chromium 2.4 µg/L, cobalt 1.8 µg/L) and the other with high metal ion concentrations (chromium 10.50 µg/L, cobalt 19.40 µg/L). Figure 4 shows the Kaplan Meier survival curve of both groups, there is no significant difference (log rank P = 0.912) between RHA (survival 89.5%) and THA (survival 90.9%) at a mean follow-up of 58 months.

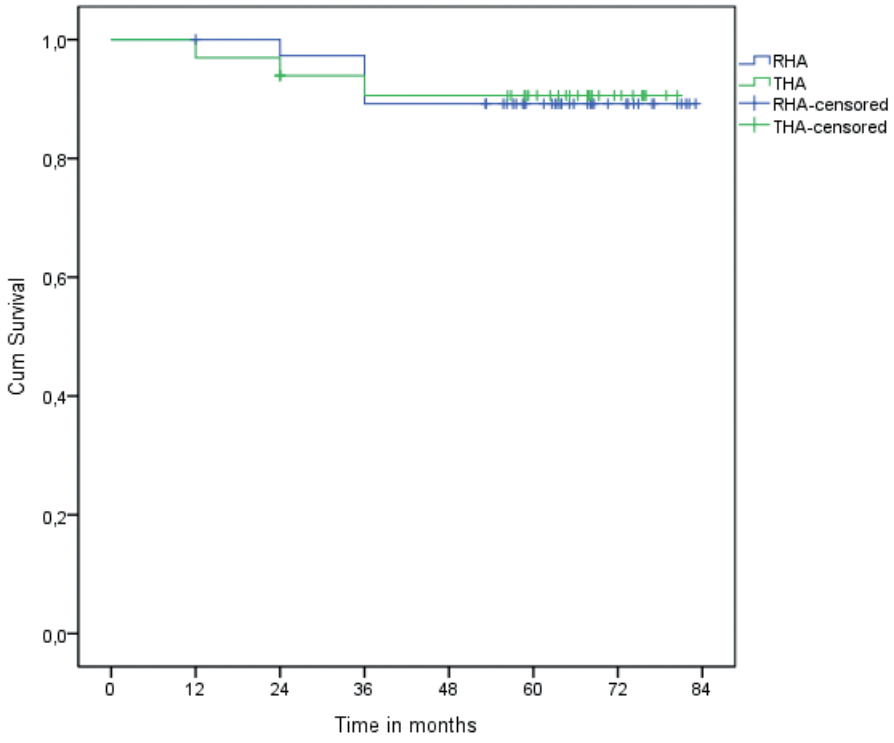


Figure 4. Kaplan Meier with revisions for any reason.

DISCUSSION

The most important finding of this 3 to 5 year follow-up of a randomized controlled trial comparing RHA and conventional THA is that no major shifts in metal ion concentrations, good clinical outcome for both groups and revisions had occurred. The majority of patients in both groups remained well functioning and highly satisfied. The numbers of revisions are comparable between groups, where pseudotumour formation was the predominant cause for revision in the RHA group (n = 2) and recurrent dislocation in the THA group (n = 2). Unexpectedly, a profound pseudotumour (n = 1) as a result of ARMD was also encountered in the 28-mm MoM THA group at time of revision for unclassified pain. Median cobalt and

chromium levels increased after implantation of both type of MoM implants with somewhat higher levels for RHA. Overall median levels stabilized after the running in phase and remained well below 2 µg/L, which is commonly recognized to be the safe zone.[16] These median cobalt and chromium levels are relatively low as compared to several other reports in the literature.[17,18]

The functional results tested by validated functional scales showed a highly significant improvement 5 years postoperatively for both RHA and THA, which corresponds with other recent mid-term follow-up studies.[19-24] Some functional outcome scores revealed a significant difference in favor of the RHA group at certain time intervals. For example, VAS satisfaction at 12 and 24 months was in favor of the RHA group, however, this difference resolved at further follow up. The OHS scored significantly better in the RHA group at 6, 24 and 36 months. The significant difference in UCLA activity score in favor of RHA, which was also preoperatively higher for RHA despite randomization, resolved at 24 months. In general, it seems that RHA patients perform slightly better than THA the first 2 years after surgery, but after 3 years no major differences in functional outcome can be found. In addition, for some encountered statistically different outcomes, like two points difference in OHS, one can argue whether the minimal clinically important difference is met. These findings correspond with earlier studies. Stulberg et al report from their large retrospective comparative study an initial advantage in HHS for RHA at 6 and 12 months, however after 24 months the results were comparable.[23] There is only one other RCT comparing RHA with a conventional THA.[25] These authors also describe initial UCLA activity scores in favor of the RHA, no differences at the 3 to 6 year and again a significant difference at 8 years. In accordance to Vendittoli et al, we found a significant difference at the early term and a not significant difference in UCLA activity score at mid-term.[21,24]

Metal ion evaluation is increasingly common after metal-on-metal arthroplasties and some articles state it serves as an indicator of bearing performance and device safety.[26] However, others question the sensitivity and specificity and state that it is not sufficient as screening measure.[27,28] Furthermore, thresholds of save zones of metal ion levels differ between studies and countries and vary between the 2.0 and the 7.0 µg/L, making it hard in decision making when to remove an implant.[16,29,30] In our study both RHA and THA groups revealed a chronological curve of cobalt and chromium blood levels representing an increase during the running-in phase of 1 year and stabilizing (cobalt) or decreasing

(chromium) levels afterwards. Regardless the implant group median metal ion levels remained well below the safety cut-off level of 2.0 µg/L for cobalt and chromium given by the Dutch Orthopaedic Society and far below the limits given by the Medicines and Healthcare products Regulatory Agency (cobalt 119 nmol/L = 7.0 µg/L; chromium 134.5 nmol/L = 7.0 µg/L).[16,30] Within this safety zone below 2.0 µg/L, overall cobalt and chromium levels were significantly higher for the RHA group, however this difference tended to fade at 5-year follow-up. Especially for chromium a gradual decrease with longer follow-up in both groups was observed.

The number of patients in this study and certainly the number of revisions for a pseudotumour is too small to draw any conclusion on a possible correlation between metal ion levels and pseudotumour formation. It can be noted however, that in two out of three revisions for a pseudotumour (one THA and two RHA patients) metal ion levels were relatively low (<2.0 µg/L), which supports Malek et al [28] and Macnair et al[27] in their conclusion that that metal ion levels cannot be counted on as screening measure.

At our 2-year follow-up we reported no revisions for pseudotumour formation, we feared a peak of revisions at 2.9 years for RHA as indicated by earlier reports in literature.[13,31] Fortunately we did not find a major shift in revision numbers so far. At 5-year follow-up six patients have had a re-operation, indicating that the mid-term revision percentage for any reason was 8% in both groups. As already described, at the 2-year follow-up study, two THA patients underwent a relatively simple insert exchange for recurrent dislocation and one RHA patient had a femoral component revision because of early aseptic loosening from avascular necrosis. Around the 3-year followup moment in three patients (one THA and two RHA patients) a symptomatic pseudotumour was encountered, which mandated revision to an alternative bearing. Interestingly one of these three pseudotumours was encountered in the conventional THA group, which indicated that this complication was not reserved for RHA only. These results are in accordance with the RCT of Vendittoli et al as they also found no significant differences in revision rates and functional results between RHA and a 28 mm MoM THA.[21] The adverse reactions to metal debris (ARMD) after a 28-mm MoM bearing as was encountered in our study are not commonly described in literature and have a lower prevalence then after large diameter MoM bearings. However, recent literature, has also recognized a 0.5–1.8% revision rate because of ARMD after 28-mm MoM hip arthroplasties, up to 10 years of follow-up.[32-34]

In spite of the strength of a true prospective randomized comparison of clinical outcome and metal ion levels between conventional THA and RHA, our study also had limitations. Since patients tended to have a profound preference for a RHA at the time of study start-up patient inclusion for randomization proved to be extremely difficult and therefore the available number of patients limited.[35] For this reason, we feel the results should be interpreted as an exploratory trial only. In addition, this profound preference might be a reason for the preoperative differences in SF-12 and UCLA activity score. On the other hand, a true randomized comparison between RHA and conventional THA is scarce and still valuable in the current debate about whether RHA should be abandoned or maintained. In addition, our results reflect rather successful results for RHA as compared to more disturbing reports in the recent literature.[15,36] Design features may have played a role. Another limitation is the absence of cross sectional imaging on all patients. Current insights show that metal ion concentrations and functional outcome seem to underestimate the prevalence of (silent) pseudotumours.[37-39] This may also be true for our study and therefore, MRI on all study patients is currently performed in a separate study protocol.

In conclusion, we feel that the absence of a clinically relevant benefit of RHA over conventional THA in this study versus the well-established concern from potential MoM bearing related adverse events does not support general use of RHA in relatively young patients. On the other hand mid-term results against THA are reassuring and for selected cases it remains a validated treatment option, in particular from its proven relatively stable concept. Patients should then be well informed preoperatively about the current concern for potential metal toxicity and be monitored accordingly, postoperatively.

REFERENCES

1. Amstutz HC, Ball ST, Le Duff MJ, et al. Resurfacing THA for patients younger than 50 years: Results of 2- to 9-year followup. *Clin Orthop Relat Res* 2007;460:159.
2. Grigoris P, Roberts P, Panousis K, et al. The evolution of hip resurfacing arthroplasty. *Orthop Clin North Am* 2005;36:125 [vii].
3. Vendittoli PA, Lavigne M, Roy AG, et al. A prospective randomized clinical trial comparing metal-on-metal total hip arthroplasty and metal-on-metal total hip resurfacing in patients less than 65 years old. *Hip Int* 2006;4:73.
4. Witzleb WC, Knecht A, Beichler T, et al. Hip resurfacing arthroplasty [German article]. *Orthopade* 2004;33:1236.
5. Amstutz HC, Beaule PE, Dorey FJ, et al. Metal-on-metal hybrid surface arthroplasty: two to six-year follow-up study. *J Bone Joint Surg Am* 2004;86-A:28.
6. Daniel J, Pynsent PB, McMinn DJ. Metal-on-metal resurfacing of the hip in patients under the age of 55 years with osteoarthritis. *J Bone Joint Surg (Br)* 2004;86:177.
7. Hing CB, Back DL, Bailey M, et al. The results of primary Birmingham hip resurfacings at a mean of five years. An independent prospective review of the first 230 hips. *J Bone Joint Surg (Br)* 2007;89:1431.
8. Treacy RB, McBryde CW, Pynsent PB. Birmingham hip resurfacing arthroplasty. A minimum follow-up of five years. *J Bone Joint Surg (Br)* 2005;87:167.
9. Brodner W, Bitzan P, Meisinger V, et al. Serum cobalt levels after metal-on-metal total hip arthroplasty. *J Bone Joint Surg Am* 2003;85-A:2168.
10. Ladon D, Doherty A, Newson R, et al. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplasty* 2004;19:78.
11. MacDonald SJ. Metal-on-metal total hip arthroplasty: the concerns. *Clin Orthop Relat Res* 2004:86.
12. Shimmin AJ, Bare J, Back D. Complications associated with hip arthroplasty. *Orthop Clin North Am* 2005;36:187.
13. Smolders JMH, Hol A, Rijnberg WJ, et al. Metal ion levels and functional results after either resurfacing hip arthroplasty or conventional metal-on-metal hip arthroplasty. *Acta Orthop* 2011;82:559.

14. Daniel J, Ziaee H, Pradhan C, et al. Blood and urine metal ion levels in young and active patients after Birmingham hip resurfacing arthroplasty. *J Bone Joint Surg Br* 2007;89-B:169.
15. Langton DJ, Jameson SS, Joyce TJ, et al. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement. *J Bone Joint Surg Br* 2010; 92-B:38.
16. Verhaar JA. The hard lesson of metal-on-metal hip implants. [Dutch article]. *Ned Tijdschr Geneeskd* 2012;156:A5564.
17. Allan DG, Trammell R, Dyrstad B, et al. Serum cobalt and chromium elevations following hip resurfacing with the Cormet 2000 device. *J Surg Orthop Adv* 2007;16:12.
18. deSouza RM, Parsons NR, Oni T, et al. Metal ion levels following resurfacing arthroplasty of the hip: serial results over a ten-year period. *J Bone Joint Surg (Br)* 2010;92:1642.
19. Issa K, Palich A, Tatevossian T, et al. The outcomes of hip resurfacing compared to standard primary total hip arthroplasty in Men. *BMC Musculoskelet Disord* 2013; 14:161.
20. Coulter G, Young DA, Dalziel RE, et al. Birmingham hip resurfacing at a mean of ten years: results from an independent centre. *J Bone Joint Surg (Br)* 2012;94:315.
21. Vendittoli P-A, Rivière C, Roy AG, et al. Metal-on-metal hip resurfacing compared with 28-mm diameter metal-on-metal total hip replacement: A randomised study with six to nine years' follow-up. *Bone Joint J* 2013;95-B:1464.
22. Nikolaou VS, Edwards MR, Bogoch E, et al. A prospective randomised controlled trial comparing three alternative bearing surfaces in primary total hip replacement. *J Bone Joint Surg (Br)* 2012;94:459.
23. Stulberg BN, Fitts SM, Bowen AR, et al. Early return to function after hip resurfacing: Is it better than contemporary total hip arthroplasty? *J Arthroplasty* 2010;25:748.
24. Vendittoli PA, Ganapathi M, Roy AG, et al. A comparison of clinical results of hip resurfacing arthroplasty and 28 mm metal on metal total hip arthroplasty: a randomised trial with 3–6 years follow-up. *Hip Int* 2010;20:1.
25. Vendittoli PA, Lavigne M, Girard J, et al. A randomised study comparing resection of acetabular bone at resurfacing and total hip replacement. *J Bone Joint Surg (Br)* 2006;88-B:997.
26. Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res* 2005;438:177.
27. Macnair RD, Wynn-Jones H, Wimhurst JA, et al. Metal Ion Levels Not Sufficient as a Screening Measure for Adverse Reactions in Metal-on-Metal Hip Arthroplasties. *J Arthroplasty* 2013;28:78.

28. Malek IA, King A, Sharma H, et al. The sensitivity, specificity and predictive values of raised plasma metal ion levels in the diagnosis of adverse reaction to metal debris in symptomatic patients with a metal-on-metal arthroplasty of the hip. *J Bone Joint Surg (Br)* 2012;94:1045.
29. Van Der Straeten C, Grammatopoulos G, Gill HS, et al. The 2012 Otto Aufranc Award: The interpretation of metal ion levels in unilateral and bilateral hip resurfacing. *Clin Orthop Relat Res* 2013;47:377.
30. No authors listed. MHRA. Medical Device Alert: All metal-on-metal (MoM) hip replacements MDA/ 2012/036; 2012.
31. De Smet K, De Haan R, Calistri A, et al. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg Am* 2008; 90(Suppl. 4):202.
32. Sugano N, Iida H, Akiyama H, et al. Nationwide investigation into adverse tissue reactions to metal debris after metal-on-metal total hip arthroplasty in Japan. *J Orthop Sci* 2014;19:85.
33. Innmann MM, Gotterbarm T, Kretzer JP, et al. Minimum ten-year results of a 28mm metal-on-metal bearing in cementless total hip arthroplasty in patients fifty years of age and younger. *Int Orthop* 2013;38:929.
34. Ebreo D, Bell PJ, Arshad H, et al. Serial magnetic resonance imaging of metal-onmetal total hip replacements. Follow-up of a cohort of 28 mm Ultima TPS THRs. *Bone Joint J* 2013;95-B:1035.
35. Bisseling P, Smolders JMH, Hol A, et al. No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty. *Acta Orthop* 2011;82:161.
36. Bosker BH, Ettema HB, Boomsma MF, et al. High incidence of pseudotumour formation after large-diameter metal-on-metal total hip replacement: a prospective cohort study. *J Bone Joint Surg (Br)* 2012;94:755.
37. Van der Weegen W, Smolders JMH, Sijbesma T, et al. High incidence of pseudotumours after hip resurfacing even in low risk patients; results from an intensified MRI screening protocol. *Hip Int* 2012;23:243.
38. Williams DH, Greidanus NV, Masri BA, et al. Prevalence of Pseudotumor in Asymptomatic Patients. *J Bone Joint Surg Am* 2011;93:2164.
39. Bisschop R, Boomsma M, van Raay J, et al. High Prevalence of Pseudotumors in Patients with a Birmingham Hip Resurfacing Prosthesis. *J Bone Joint Surg Am* 2013; 95:1554.

Surg (Br) 2012;94:459.

23. Stulberg BN, Fitts SM, Bowen AR, et al. Ear
than contemporary total hip arthroplasty? *J Arth*

24. Vendittoli PA, Ganapathi M, Roy AG, et al. A compa
arthroplasty and 28 mm metal on metal total hip arth
years follow-up. *Hip Int* 2010;20:1.

25. ittoli PA, Lavigne M, Girard J, et al. A randomised study
bone rfacing and total hip replacement. *J Bone Joint S*

26. Back DL, Y DA, Shimmin AJ. How do serum cobalt an
metal-on-metal h rfacing? *Clin Orthop Relat Res* 2005;

27. Macnair RD, Wynn-Jo Wimhurst JA, et al. Metal
Screening Measure for Adver ctions in Metal-on-Metal
2013;28:78.

CHAPTER 4

Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data?

José M.H. Smolders, Pepijn Bisseling, Annemiek Hol, Catherine Van Der Straeten, B. Willem Schreurs, Job L.C. Van Susante

Hip Int. 2011 Sep-Oct;21(5):587-95.

ABSTRACT

Metal ions generated from joint replacements are a cause for concern. There is no consensus on the best surrogate measure of metal ion exposure, and both serum and whole blood measurements are used in clinical practice. This study provides a guideline for interpretation of metal ion analysis in clinical practice.

In a prospective trial comparing resurfacing hip arthroplasty (RHA) with a conventional metal-on-metal (MoM) total hip arthroplasty (THA) cobalt and chromium levels were determined for whole blood and serum in 343 paired samples at regular intervals up to 24 months postoperatively.

Cobalt whole blood and serum levels increased significantly after both procedures. Cobalt concentrations were significantly higher for the RHA group compared to the THA group, at 3, 6 and 12 months, for whole blood and serum. At 24 months cobalt levels decreased and differences between RHA and THA were no longer significant. In contrast, chromium whole blood levels remained significantly higher for RHA until 24 months.

Whole blood and serum levels could not be used interchangeably. The mean differences for cobalt and chromium between blood and serum values were +0.13 µg/L and -0.91 µg/L respectively. Regression analysis provided a formula for conversion from serum to blood of 0.34+[0.88*Co serum] for cobalt and 0.14+[0.58*Cr serum] for chromium, with an acceptable prediction error below ±1.0 µg/L. Cobalt and chromium levels were significantly higher for RHA versus THA, especially during the run-in phase of one year. Overall, the metal ion levels were well below 5 µg/L. We cannot recommend the use of whole blood over serum measurements or vice versa. The provided conversion formula between whole blood and serum in combination with the presented practical guidelines may be useful for clinical practice.

INTRODUCTION

Resurfacing hip arthroplasty (RHA) has been re-introduced as an attractive bone preserving treatment option for young patients with osteoarthritis. In addition, 'in vitro' studies on the metal-on-metal (MoM) articulation revealed a 20-fold reduction of volumetric wear in comparison with metal-on-polyethylene.[1,2] The relatively small size of these metal particles (6-834nm) accounts for this decrease in volumetric wear, since the total number of particles is higher.[3] Liberated metal ions may bind to proteins and cells and can be transported elsewhere, resulting in elevated levels in blood, serum and urine.[2,4-7] These elevated systemic metal ion levels are a cause for concern. Reports of hypersensitivity reactions [8,9], osteolysis [9,10] and the growth of liquid or solid soft tissue reactions [11,12] are available. There is increasing evidence that elevated levels of metal ions (especially cobalt) may have adverse long term systemic effects including polyneuropathy, cardiomyopathy and hypothyroidism.[13,14] The uncertainty about the consequences of these elevated metal ion levels has raised concerns and diminished the use and acceptance of MoM bearings. In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency (MHRA) has produced guidelines regarding the monitoring of systemic ion levels, and assay is recommended in cases with pain, adverse radiological abnormalities and small component head size. Metal ion measurements and a knowledge of their interpretation have thus become important.

Various matrices, such as whole blood (WB), serum (SE) and urine can be used. Analyses in whole blood or serum is preferable, since urine requires a 24-hour collection and the levels seem to be more variable due to variation in hydration of the patient.[15] Metal ion levels after different MoM hip implants have been reported.[16,19] However, most studies report on either metal ion concentrations in whole blood or serum, and data on repeated measurements over time are scarce, resulting in a lack of knowledge of how levels evolve over time. There may be superiority of serum over whole blood measurements, but whether these two levels can be correlated is not fully understood.

The aim of our study was to present prospective follow-up of cobalt and chromium levels in both whole blood and serum in a group of patients with a RHA versus a conventional MoM total hip arthroplasty (THA). In addition, a conversion formula was generated to calculate serum from whole blood metal ion levels and practical guidelines were developed for clinical use in the interpretation of metal ion levels.

PATIENTS AND METHODS

Between May 2007 and April 2010 97 patients were prospectively followed in either a randomised controlled trial (RCT) comparing a RHA to a conventional MoM THA, or they participated in the cohort of RHA patients. Approval for both RCT and cohort was obtained from the regional ethics committee of the Radboud University Nijmegen Medical Centre (LTC 419-071206). All patients agreed to sign an informed consent.

All patients under the age of 65 were asked to participate in the ongoing RCT. Patients who preferred not to participate but who requested RHA were followed in a separate cohort. Cobalt and chromium levels were prospectively analysed in both whole blood and serum at consecutive time intervals. In the RHA group a resurfacing prosthesis was implanted with both components made of a cast, heat treated solution-annealed Co-Cr alloy (Conserve plus®; Wright Medical Technology, Arlington, Tennessee, USA).

Mean resurfacing femoral head size was 48 mm (range 42-54). In the THA group, an uncemented tapered stem and a threaded titanium cup with a polyethylene insert with a metal liner was inserted (Zweymuller Classic; Zimmer Orthopaedics, Warsaw, Indiana, USA) together with a metal 28-mm head (Metasul®; Zimmer Orthopaedics, Warsaw, Indiana, USA). A total of 343 paired whole blood and serum specimen were collected pre-operatively and at 3, 6, 12 and 24 months in 97 patients. Ninetytwo patients had a follow-up of more than 3 months. Metal ion levels below the detection limit of 0.5 µg/L were excluded in the statistical evaluation of the correlation between whole blood and serum levels and in generating a conversion formula. After exclusion of these baseline levels below the detection limit 213 cobalt specimens and 191 chromium specimens remained in 79 and 72 patients respectively. Demographic data of the study population and specimens are given in Table I and II.

Table I. Demographic data of the study population

RHA	(N=60)	THA (N=32)	p-value
Gender (men/women)	36/24	20/12	1.000 [a]
Median age in years (range)	55.3 *(25-65)*	59.1 *(36-65)*	0.106 [b]
Mean body mass index in Kg/m^2 (SD)	26.6 *(4.8)*	27.9 *(5.2)*	0.243 [c]
Preoperative diagnosis (OA/AVN/CHD)	57/1/2	30/0/2	0.786 [d]
Charnley category (A/B1/B2)	36/14/10	23/5/4	0.285 [d]
Mean operating time in minutes (SD)	78.1 *(12.9)*	55.5 *(12.0)*	<0.001 [c]
Median blood loss in mL (range)	300 *(100-600)*	275 *(100-900)*	0.653 [b]

OA: Osteoarthritis, AVN: Vascular necrosis, CHD: Congenital hip dysplasia
[a] Fisher's exact probability test, [b] Mann-Whitney U test, [c] Student's t-test. [d] Kruskall-Wallis test

Table II. Demographic data of specimens

	Cobalt (N=79)	Chromium (N=72)
Gender (men/women) (p-value)	48/31 (0.056)	39/33 (0.480)
Median femoral component size of RHA (range)	48 (42-54)	48 (42-54)
Total number of specimen	343	343
Number of specimen included	213	191
Below detection limit	130	152
Conserve/Metasul/Bilateral/No prosthesis	149/58/53/6	147/40/45/4

Cobalt and chromium blood levels

Blood samples were collected in metal-free vacutainers, the first 5 ml blood being discarded to eliminate metal contamination from the needle. A 6 ml BD 'EDTA' and a 5 ml 'SST II Advance' vacutainer system (Franklin Lakes, New Jersey, USA) was used for blood collection. After blood collection the tube with clot activator was set at rest for a minimum of 30 minutes and was then centrifuged at 3600 rpm for ten minutes. Both tubes were stored

at a maximum of 4°C and sent within 7 days to the laboratory of Toxicology of the University Hospital Ghent (Belgium) for analysis. The metal ion levels in serum and whole blood were determined using an inductively-coupled plasma mass spectrometer (ICP-MS) on a Perkin Elmer Elan DRCe, equipped with a standard cross-flow nebuliser and a Dynamic Reaction Cell (Perkin Elmer SCIEX, Canada).

Statistical analysis

Since metal ion data are not normally distributed they are represented by the median, and a non-parametric test (Mann-Whitney U) was used for analysis. The agreement between whole blood and serum levels was assessed with mean difference, regression analysis and the Blandand-Altman limits-of-agreement between methods of measurement with multiple observations per individual, as is proposed by Bland-and-Altman.20 In this study several measurements in the same patients were used. Therefore we used the modification from Bland-Altman with adjustment for the repeated measurements.[21]

The multiple observations per individual can have influence on the regression analysis. Therefore prior to this analysis a mixed model analysis was used to analyse the influence of the repeated measurements on the linear regression. The Null Model Likelihood Ratio Test showed a p-value of > 0.05 for all tests, indicating that there is no significant difference between a regression with ignorance of the repeated measurements and the regression with adjustment for the repeated measurements. As a result the simple linear regression with the equation 'whole blood level = $\alpha+\beta$*serum level' was used for all analyses in this study. To validate our regression equation we randomly split the database into two. The patients in the first section were used to calculate a regression equation which could be tested on the second section. The data was processed in SPSS (Version 15.0 SPSS Inc. Chicago, IL) and analysed for statistical differences. Statistical significance was set at $p \leq 0.05$.

RESULTS

RHA versus THA metal ion levels

Patient characteristics are described in Table I. The mean operating time was longer for RHA ($p < 0.001$), but median blood loss was equal between the two groups. The concentrations of cobalt and chromium in whole blood and serum for RHA versus THA for each time interval are summarised in Table III and Figures 1a and 1b. Baseline preoperative cobalt and chromium concentrations were, as expected, below the detection level of 0.5 µg/L for both groups. Cobalt whole blood and serum levels increased after implantation of a RHA ($p < 0.001$) and a THA ($p = 0.015$ (WB) and $p = 0.002$ (SE)).

Cobalt concentrations were higher for RHA compared to THA at 3, 6 and 12 months for whole blood ($p < 0.001$, $p = 0.001$, $p = 0.026$) and serum ($p < 0.001$, $p < 0.001$, $p = 0.007$). At 24 months cobalt levels stabilised and the initially statistically significant difference between RHA and THA could no longer be detected for whole blood ($p = 0.082$) and serum ($p = 0.530$). Postoperative chromium levels of RHA patients increased compared to the preoperative levels for whole blood and serum ($p < 0.001$). The THA patients showed a solitary increase for serum ($p < 0.001$), while whole blood concentrations remained stable ($p = 0.243$). Chromium concentrations were higher for RHA at 3, 6 and 24 months for whole blood ($p < 0.001$, $p < 0.001$, $p = 0.021$), and at all follow-up intervals for serum ($p < 0.001$).

Whole blood versus serum

Demographics of specimen-specific patient data are given in Table II. The mean difference between serum and whole blood was +0.13 µg/L for cobalt (95%-CI:0.03;0.22) and -0.91 µg/L for chromium (95%-CI:-1.05;-0.77). There was a statistically significant difference between whole blood and serum levels for cobalt ($p = 0.01$) and chromium ($p < 0.001$). Despite this difference, cobalt and chromium levels in whole blood and serum were highly correlated: cobalt $R = 0.936$ ($p < 0.001$) and chromium $R = 0.937$ ($p < 0.001$). A Bland-Altman analysis showed limits-of-agreement of +1.5 µg/L and -1.25 µg/L with a mean difference of +0.13 µg/L for cobalt (Figure 2a). This means that cobalt levels in whole blood are on average +0.13 µg/L higher compared to serum and that 95% of these differences between blood and serum levels appeared to be between +1.5 µg/L and -1.25 µg/L. For chromium the correlation between whole blood and serum levels was obscured by an

increase in difference at higher mean concentrations. There was a mean difference between whole blood and serum of -0.91 µg/L with relatively wide limits-of-agreement between +0.95 µg/L and -2.85 µg/L. The tendency of an increase in difference between whole blood and serum at higher mean concentrations is visualised by a diagonal trend in the Bland-Altman plot (Figure 2b). We calculated a conversion formula for serum metal ion levels into whole blood metal ion levels by regression analysis. The following formula was established for Cobalt (Co) and chromium (Cr):

Co whole blood = 0.34+[0.88*Co serum]
Cr whole blood = 0.14+[0.58*Cr serum]

Validation of prediction model blood versus serum

In order to validate the conversion formula, we randomly divided our database in two. A similar regression analysis on half of the database provided a conversion formula which was subsequently tested on the second half of the database. The newly obtained conversion formulae were Co whole blood = 0.29+[0.89*Co serum] and Cr whole blood = 0.21+[0.54*Cr serum]. Serum levels from the second half of the database were used to predict whole blood levels, and compared to the actual measured values. The Bland-Altman test was computed as the difference between the measured and predicted value (Figure 3a and b). The mean difference between measured and predicted values of cobalt and chromium was 0.0 µg/L. Limits-of-agreement for the difference between predicted and measured cobalt whole blood levels were +0.77 µg/L and -0.84 µg/L. In relation to chromium these limits were +0.92 µg/L and -0.98 µg/L. There was no difference between predicted and actual measured whole blood values of cobalt (p = 0.411) and chromium (p=0.561).

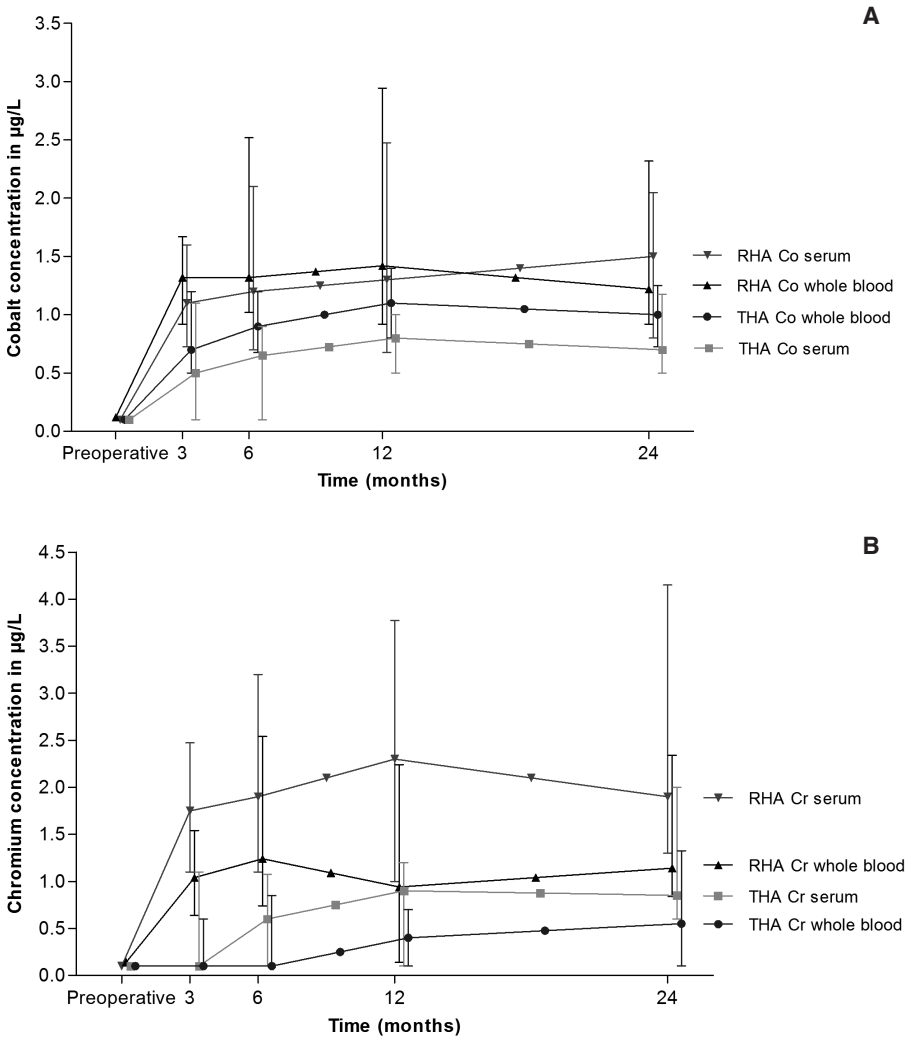


Figure 1.

(A) Error-plot (median and IQR) cobalt concentrations in whole blood and in serum in µg/L.

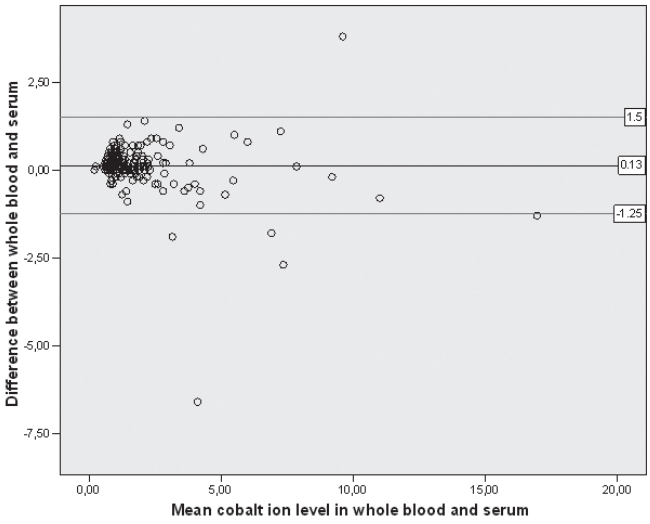
(B) Error-plot (median and IQR) chromium concentrations in whole blood and serum in µg/L.

Table III. Cobalt and Chromium concentrations.

	Preoperative		6 months		12 months		24 months	
	RHA	THA	RHA	THA	RHA	THA	RHA	THA
Cobalt	(N=60)	(N=32)	(N=51)	(N=30)	(N=42)	(N=23)	(N=21)	(N=8)
WB	0.10 (0.1-2.7)	0.10 (0.1-1.8)	1.30[a] (0.1-10.6)	0.90[a] (0.1-4.0)	1.40[a] (0.6-11.5)	1.10[a] (0.1-2.2)	1.20 (0.7-16.3)	1.00 (0.1-1.6)
SE	0.10 (0.1-2.6)	0.10 (0.1-1.3)	1.20[a] (0.1-11.4)	0.65[a] (0.1-4.1)	1.30[a] (0.1-11.4)	0.80[a] (0.1-1.9)	1.50 (0.7-17.6)	0.70 (0.1-1.4)
Chromium	(N=60)	(N=32)	(N=51)	(N=30)	(N=42)	(N=23)	(N=21)	(N=8)
WB	0.10 (0.1-4.2)	0.10 (0.1-0.8)	1.20[a] (0.1-5.9)	0.10[a] (0.1-2.9)	0.90 (0.1-6.0)	0.40 (0.1-1.9)	1.10[a] (0.1-8.4)	0.55[a] (0.1-2.1)
SE	0.1 (0.1-2.7)	0.1 (0.1-2.9)	1.90[a] (0.1-8.8)	0.60[a] (0.1-4.9)	2.30[a] (0.1-10.2)	0.90[a] (0.1-2.9)	1.90[a] (0.9-14.4)	0.85[a] (0.1-3.4)

Values (µg/L) are given as the median (range). WB: whole blood, SE: serum
[a] Significant difference between RHA and THA (Mann-Whitney signed-rank)

A



B

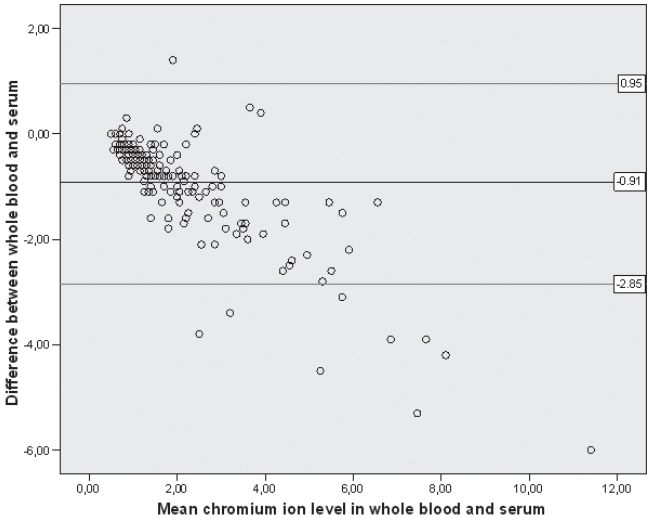
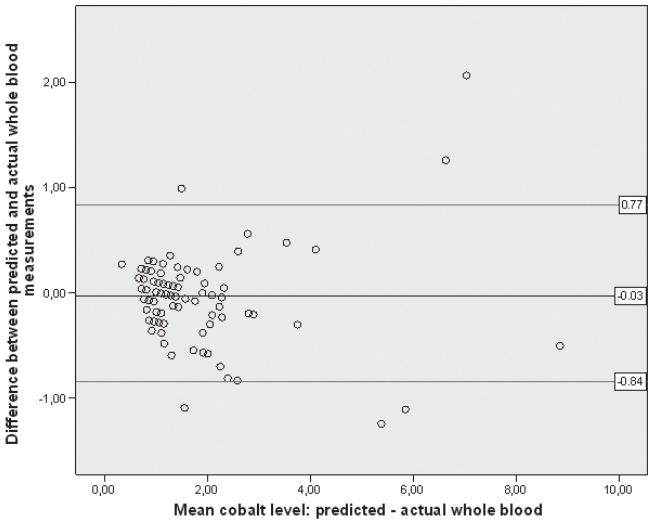


Figure 2.

(A) Cobalt standard Bland-Altman plot

(B) Chromicum standard Bland-Altman plot. In both graphs the black line illustrates the mean difference between metal ion levels in serum and whole blood and the two gray parallel lines illustrate the 1.96 standard deviation of this difference or 'limits-of-agreement'.

A



B

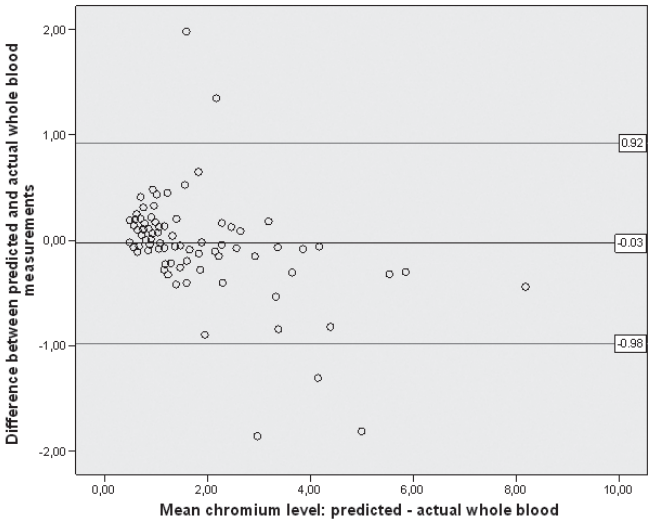


Figure 3.

(A) Predicted cobalt levels compared to the actual blood levels

(B) Predicted chromium levels compared to the actual blood levels. In both graphs the black line illustrates the mean difference between predicted and real metal ion levels in serum and whole blood and the two gray parallel lines illustrate the 1.96 standard deviation of this difference or 'limits-of-agreement'.

DISCUSSION

The evaluation of metal ion levels is becoming increasingly important after a MoM hip arthroplasty and serves as an indicator of bearing performance and device safety.[19] In this study, RHA revealed a higher initial increase in cobalt and chromium concentrations than a conventional MoM 28-mm THA. After a run-in phase, this difference in cobalt levels between the two groups resolved, but chromium levels were still higher for the RHA group. Because cobalt is known to be a relatively toxic ion [13,22], it is important to note that cobalt levels decrease after a run-in phase of 12 months. It is clear from our observations that increased metal ion levels are not exclusively seen in RHA patients, and over time metal ion levels after RHA may approach values following a MoM THA. These findings are consistent with previous reports; which suggest that after 5 years there is no difference in metal ion concentrations following large-diameter resurfacing and a small-diameter MoM THA.[17] Unlike some reports following the use of a variety of RHA devices, the metal ion levels following both RHA and THA used in our study appeared to be rather low.[16,17,19] Implant-related differences are present in metal ion release and this should be taken into account as one of the confounding factors in the interpretation of our results. Furthermore, it has to be recognised that the mechanism and source of metal debris may also be different for RHA compared to MoM THA. In general metal ions and particles are generated both by wear from the articulation and by corrosion. In addition to metal ion release from the bearings, a THA may create metal debris from the taper junction with the head. This may thus have influenced metal ion concentrations in peripheral blood in the THA group However, the source of metal ion release should not influence the relationship between metal ion levels in serum versus whole blood as evaluated in our study. Metal ion levels may be influenced by renal excretion, protein binding and transport, and extremely high levels of cobalt may occur in patients with renal dysfunction, and therefore MoM bearings are contraindicated in these patients.[23] High levels can also be related to other sources of metal ion release, such as mechanical heart valves, orthodontic implants, medical or nutritional supplements containing metal ion 'equivalents' or environmental and/or occupational sources of metal contamination. All patients in our study were carefully monitored for the potential presence of these other sources of metal ions. These confounding factors should always be taken into consideration when confronted by high metal ion levels, and remain an obstacle in the interpretation of metal ion levels.

Regarding the differences between serum and whole blood, cobalt serum levels were slightly lower or equivalent to whole blood, which was represented by a mean difference of only +0.13 µg/L. For chromium, serum levels were relatively high compared to whole blood, indicated by a mean difference of -0.91 µg/L. Our results correspond with earlier data from Walter et al, who found little difference between whole blood and serum for cobalt, but higher serum levels compared to whole blood for chromium.[6] Studies that examine the difference between metal traces in whole blood and serum are rare. Daniel et al [7] studied the suitability of whole blood and serum for measurement of ion levels, but the limits-of-agreement between whole blood and serum for cobalt and chromium were relatively wide as compared to our data with +3.8 µg/L; -2.2 µg/L for cobalt and +8.4 µg/L; -4.2 µg/L for chromium. This finding may be explained by differences in collection and processing of the samples, and the fact that Daniel et al studied a group of miscellaneous types of resurfacing implants each with unique metallurgy.[24,25] Daniel et al suggested whole blood as a superior matrix over serum metal ion measurements [7], but from our data we cannot recommend whole blood over serum or 'vice versa'. From a practical point of view, the use of whole blood may be preferred, since whole blood can be sent to the laboratory without separation of serum, a step which can introduce pollution to the sample. The option of a conversion formula to extrapolate serum to whole blood metal ion levels is attractive for obvious reasons. Based on the wide limits-of-agreement of the Bland-Altman plot we do not believe that the two blood fractions can be used interchangeably. However, conversion between whole blood and serum remains possible. The conversion formulae, as provided in this study, can be used with limits-of-agreement that are within acceptable range (Figure 3a and b). For both metal ions the whole blood and serum levels could be predicted from one another with a prediction error below 1.0 µg/L. The prediction error is obtained from testing on a homogeneous group of patients, and verification on a heterogeneous group might be helpful. The conversion formula is best used for the lower boundary of metal ion levels and may offer reassurance to the clinician in interpreting metal ion levels. The provided levels can subsequently be balanced to the upper acceptable limits. Higher values cannot be predicted without accepting a greater prediction error, but we believe that prediction of these values from serum to whole blood is of less clinical significance since the values are usually already in the pathological range, and indicative of malfunctioning of the implant.

There are some weaknesses in our study. The number of available samples at 24 months was limited, which may have contributed to the observed non-significant difference in cobalt levels between both implants. Further follow-up of these patients will eventually resolve this. Cobalt has a smaller variability compared to chromium, but is recognised to be more toxic both in particle and ion form. It is therefore important to follow cobalt ion levels closely. We also recognise some limitations in the conversion formulae presented. The conversion formula is particularly valuable for the concentrations in the range of 2-5 µg/L, both because its prediction error is lowest in the lower range and because the lower values are of clinical importance for the evaluation of implant performance. Since the vast majority of metal ions should be below 5 µg/L it may not be clinically relevant to be able to predict a serum or whole blood level knowing that it is already in the higher range. The formulae can be used for reassurance in clinical practice. A low serum level, for example, will never be correlated with a high whole blood level. Only one clinical sample (either whole blood or serum) can be used to conform to safety guidelines referring to serum or whole blood levels.

It is extremely important in clinical practice to know the upper acceptable levels for metal ions. The best-defined reference values are the "exposure equivalent of carcinogenic substances" (EKA values) [26] for industrial workers and the Mayo Medical Laboratories interpretive handbook.[27] The upper limits are defined for cobalt at 5 µg/L in whole blood and for chromium at 17 µg/L in erythrocytes (no whole blood upper limits reported).[26] In addition to these reference values, De Smet et al analysed metal ion levels in patients with a well functioning versus a malfunctioning RHA and proposed that serum cobalt and chromium levels up to respectively 4.4 µg/L (odds ratio for revision 6.0) and 5.1 µg/L (odds ratio for revision 4.3) are acceptable as upper limits.[28] Metal ion levels higher than twice these upper limits are very likely to be associated with poor clinical outcome.[28] The median ion levels of our study are well below this limit, although a few outliers were still encountered. The North Tees group (UK) state that patients with cobalt values between 2 and 5 µg/L have to be followed clinically and patients with cobalt values above 5 µg/L have to be evaluated with cross-sectional imaging.[29] In patients with clearly elevated levels, revision should be considered or anticipated.

We have summarised our results together with data from the literature in an attempt to produce some guidelines (Tab. IV) which may help the orthopedic surgeon regarding

the use and interpretation of metal ion levels in patients with a MoM hip arthroplasty. It is important to emphasise again that these guidelines can only be seen as an aid to the clinician in decision making and certainly not as an absolute reference tool. Numerous limitations exist, but since the topic of the interpretation of metal ion levels is becoming increasingly important we believe our study may help the clinician towards understanding of this difficult topic.

Table IV. Practical guidelines fort he interpretation of metal ion levels in patients with a MoM hip arthroplasty.

Type of Analysis	No superiority of whole blood or serum; whole blood may be favored for practical reasons depending on local preference.
	Inductively-coupled plasma mass spectrometer (ICP-MS) method of first choice.
Resurfacing (RHA) versus Conventional (THA)[1]	Metal ion levels are significantly higher for RHA versus THA. This difference decreases after the run-in phase, in particular for cobalt.
Metal ions measurement	Serum ≠ whole blood
	Toxicity: Cobalt > Chromium
Cobalt	Serum > and < whole blood
	Co blood = Co serum + 0.13 µg/L (95%-CI:0.03;0.22) Conversion formula (prediction error <1 µg/L): Co whole blood = 0.34+[0.88*Co serum]
Chromium	Serum (in general) > whole blood
	Cr blood = Cr serum - 0.91 µg/L (95%-CI:-1.05;-0.77). Conversion formula (prediction error <1 µg/L): Cr whole blood = 0.14+[0.58*Cr serum]
Confounding Factors	Renal impairment 'Contamination' by nutritional supplements, medication, other metal implants Implant type and positioning
High levels	Associated with an increased risk of a malfunctioning implant. Close monitoring is indicated with levels :
	Cobalt serum concentration >4.4 µg/L Chromium serum concentration >5.1 µg/L

[1] This conclusion applies for the implants used in this study and may differ for other implants.

REFERENCES

1. Amstutz HC, Campbell P, McKellop H, et al. Metal on metal total hip replacement workshop consensus document. *Clin Orthop Relat Res* 1996; 329 (suppl): S297-303.
2. Sieber HP, Rieker CB, Kottig P. Analysis of 118 second-generation metal-on-metal retrieved hip implants. *J Bone Joint Surg Br* 1999; 81: 46-50.
3. Doorn PF, Campbell PA, Worrall J, Benya PD, McKellop HA, Amstutz HC. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res* 1998; 42: 103-11.
4. Case CP, Langkamer VG, James C, et al. Widespread dissemination of metal debris from implants. *J Bone Joint Surg Br* 1994; 76: 701-12.
5. Merritt K, Brown SA. Distribution of cobalt chromium wear and corrosion products and biologic reactions. *Clin Orthop Relat Res* 1996; 329 (suppl): S233-43.
6. Walter LR, Marel E, Harbury R, Wearne J. Distribution of chromium and cobalt ions in various blood fractions after resurfacing hip arthroplasty. *J Arthroplasty* 2008; 23: 814-21.
7. Daniel J, Ziaee H, Pynsent PB, McMinn DJ. The validity of serum levels as a surrogate measure of systemic exposure to metal ions in hip replacement. *J Bone Joint Surg Br* 2007; 89: 736-41.
8. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. *J Biomed Mater Res* 2001; 56: 427-36.
9. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005; 87: 28-36.
10. Park yS, Moon yW, Lim SJ, yang JM, Ahn G, Choi yL. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am* 2005; 87: 1515-21.
11. Boardman DR, Middleton FR, Kavanagh TG. A benign psoas mass following metal-on-metal resurfacing of the hip. *J Bone Joint Surg Br* 2006; 88: 402-4.
12. Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* 2008; 90: 847-51.
13. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br* 2007; 89: 567-73.

14. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, yamada M. Polyneuropathy caused by cobalt–chromium metallosis after total hip replacement. *Muscle Nerve* 2010; 42: 140-3.
15. MacDonald SJ, Brodner W, Jacobs JJ. A consensus Paper on Metal Ions in Metal-on-Metal Hip Arthroplasties. *The Journal of Arthroplasty* 2004; 19 (suppl 3): 12-6.
16. Antoniou J, Zukor DJ, Mwale F, Minarik W, Petit A, Huk OL. Metal ion levels in the blood of patients after hip resurfacing: A comparison between twenty-eight and thirty-six-millimeter-head metal-on-metal prostheses. *J Bone Joint Surg Am* 2008; 90 (suppl 3): 142-8.
17. Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N. Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? *Clin Orthop Relat Res* 2010; [Epub].
18. Garbuz D, Tanzer M, Greidanus N, Masri B, Duncan C. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: A randomized clinical trial. *Clin Orthop Relat Res* 2010; 468: 318-25.
19. Back DL, young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res* 2005; 438: 177-81.
20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; 1: 307-10.
21. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat* 2007; 17: 571-82.
22. Kwon yM, Xia Z, Glyn-Jones S, Beard DJ, Gill HS, Murray DW. Dose-dependent cytotoxicity of clinically relevant cobalt nanoparticles and ions on macrophages in vitro. *Biomed Mater* 2009; 4: [Epub].
23. Hur CI, yoon TR, Cho SG, Song EK, Seon JK. Serum ion level after metal-on-metal THA in patients with renal failure. *Clin Orthop Relat Res* 2008; 466: 696-9.
24. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell PA, De Smet K. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg Br* 2008; 90: 1291-7.
25. Griffin W, Nanson C, Springer B, Davies M, Fehring T. Reduced articular surface of one-piece cups: A cause of runaway wear and early failure. *Clin Orthop Relat Res* 2010; 468: 2328-32.
26. Morgan MS, Schaller KH. An analysis of criteria for biological limit values developed in Germany and in the United States. *Int Arch Occup Environ Health* 1999; 72: 195-204.

27. No authors listed. Serum Cobalt (80084) and Serum Chromium (8638) New England, Massachusetts: Mayo Medical Laboratories; 2010; Available from: http://www.mayomedicallaboratories.com/ test-catalog/alphabetical/C.
28. DeSmet KA, Campbell PA, Van Orsouw M, Gill HS. Interpretation of metal ion levels after metal-on-metal resurfacing. Proceedings AAOS 2010; Poster No: P100.
29. Langton DJ, Jameson SS, Joyce TJ, et al. Accelerating failure rate of the ASR total hip replacement secondary to taper junction failure. *J Bone Joint Surg Br* 2011; 93: in press.

of clinically relevant cobalt nano
2009; 4: [Epub].
23. Hur CI, yoon TR, Cho SG, Song EK, Seon JK.
patients with renal failure. *Clin Orthop Relat Res* 20
24. De Haan R, Pattyn C, Gill HS, Murray DW, Campbell
inclination of the acetabular component and metal ion leve
ement. *J Bone Joint Surg Br* 2008; 90: 1291-7.
25. Griffi anson C, Springer B, Davies M, Fehring T. Reduc
cups: A cau unaway wear and early failure. *Clin Orthop*
26. Morgan MS, Sch KH. An analysis of criteria for biolog
Germany and in the U tates. *Int Arch Occup Environ H*

CHAPTER 5

Metal ion levels in patients with a lumbar metal-on-metal total disc replacement. Should we be concerned?

P. Bisseling, D. J. Zeilstra, A. M. Hol,
J. L. C. van Susante

J Bone Joint Surg [Br] 2011;93-B:949-54.

ABSTRACT

The purpose of this study was to evaluate whether concerns about the release of metal ions in metal-on-metal total hip arthroplasty (THA) should be extended to patients with metalbearing total disc replacements (TDR).

Cobalt and chromium levels in whole blood and serum were measured in ten patients with a single-level TDR after a mean follow-up of 34.5 months (13 to 61) using inductively-coupled plasma mass spectrometry. These metal ion levels were compared with preoperative control levels in 81 patients and with metal ion levels 12 months after metal-on-metal THA (n = 21) and resurfacing hip replacement (n = 36). Flexion-extension radiographs were used to verify movement of the TDR.

Cobalt levels in whole blood and serum were significantly lower in the TDR group than in either the THA ($p = 0.007$) or the hip resurfacing group ($p < 0.001$). Both chromium levels were also significantly lower after TDR versus hip resurfacing ($p < 0.001$), whereas compared with THA this difference was only significant for serum levels ($p = 0.008$). All metal ion levels in the THA and hip resurfacing groups were significantly higher than in the control group ($p < 0.001$). In the TDR group only cobalt in whole blood appeared to be significantly higher ($p < 0.001$). The median range of movement of the TDR was 15.5° (10° to 22°).

These results suggest that there is minimal cause for concern about high metal ion concentrations after TDR, as the levels appear to be only moderately elevated. However, spinal surgeons using a metal-on-metal TDR should still be aware of concerns expressed in the hip replacement literature about toxicity from elevated metal ion levels, and inform their patients appropriately.

INTRODUCTION

Total disc replacement (TDR) is one surgical procedure used to treat degenerative disc disease. The theoretical advantage of TDR over spinal fusion is that movement is preserved at the involved level and accelerated degeneration of the adjacent segment is prevented.[1-3] As found in any joint replacement, the bearing surfaces of the implant might wear and release particles. Ideally, any volumetric wear should be as low as possible: metal-on-metal (MoM) articulations were introduced in an attempt to achieve this goal. At the hip, despite the relatively low volumetric wear of well-positioned MoM articulations compared with polyethylene bearings, the total number of particles released is much higher.[4,5] These particles measure between 6 nm and 834 nm in diameter[4] and are transported throughout the body, resulting in elevated levels of cobalt and chromium ions in blood and urine.[6-11]

There is increasing concern in the literature on MoM hip replacement about the potentially hazardous side-effects of these elevated metal ion levels. Numerous studies, especially on MoM hip resurfacings, have reported serious adverse events, including implant-induced hypersensitivity reactions,[12-14] osteolysis,[13,15] pseudotumour formation[16,17] and focal periprosthetic soft tissue necrosis.[13,17,18] Such adverse events frequently demand relatively early revision. In the United Kingdom these studies have led to an official alert from the Medicines and Healthcare products Regulatory Agency (MHRA), which suggests that metal ion levels should be measured in patients with a MoM hip replacement if they have features which place them at risk of an adverse reaction or pain.[19]

By comparison, very little attention has been paid to this phenomenon in spinal surgery. A search of the literature revealed only two single-centre studies on increased metal ion levels after an MoM TDR[20,21] They concluded that metal ion levels in patients with an MoM TDR are similar to those found after MoM hip replacement, which is a cause for concern given the official alert regarding MoM hip replacement. Accordingly, further evaluation of metal ion levels in patients with a TDR are required.

In this study we evaluated cobalt (Co) and chromium (Cr) ion levels in whole blood and serum of patients with an MoM TDR and compared these with levels from an ongoing trial comparing metal ion levels after hip resurfacing *versus* conventional MoM total hip arthroplasty (THA).

Table I. Demographic data of the control, total disc replacement (TDR), hip resurfacing and total hip replacement (THA) subgroups (median, range)

	Control (n = 81)	TDR (n = 10)	Hip resurfacing (n = 36)	THA (n = 21)	p-value*
Median age (yrs)	57 (34 to 64)	43 (25 to 49)	55 (24 to 64)	59 (42 to 64)	< 0.001
Median follow-up (mths)	n/a†	34.5 (13 to 61)	12 (12 to 12)	12 (12 to 12)	< 0.001
Gender					
Male	47	1	21	13	0.188‡
Female	34	9	15	8	
Median body mass index	26 (20 to 41)	24 (20 to 28)	26 (21 to 32)	27 (20 to 41)	0.133
Median blood loss (cc)	n/a	200 (53 to 1100)	300 (0 to 600)	300 (0 to 900)	0.522
Median duration operation (mins)	n/a	90 (76 to 110)	79 (58 to 122)	60 (37 to 76)	< 0.001

* Kruskal-Wallis test, unless otherwise stated
† n/a, not available
‡ Pearson chi-squared test

PATIENTS AND METHODS

Between January 2004 and June 2010, cobalt and chromium ion levels in whole blood and serum were prospectively assessed in an ongoing randomised controlled trial (RCT) comparing hip resurfacing with conventional MoM THA, and in a prospective cohort of patients with a hip resurfacing arthroplasty of the hip.[22,23] Patients received either a Conserve Plus resurfacing (Wright Medical Technology, Arlington, Tennessee) with a median femoral head diameter of 49 mm (42 to 54) or an uncemented metal-bearing Zweymuller THA (Zimmer Orthopaedics, Warsaw, Indiana) with a 28-mm Metasul head. Metal ion levels in patients from these two cohorts were available at several intervals. For this study the 12-month data from patients with a unilateral hip replacement were used, as the metal ion levels are known to be elevated during a running-in phase of approximately 6 to 12 months, after which they stabilise.[5,8,21,24] The baseline metal ion levels of all these patients were assessed preoperatively and regarded as controls.

The cobalt and chromium ion levels were also determined in ten consecutive patients with a single-level MoM Maverick TDR (Medtronic Sofamor Danek GmbH, Köln, Germany), undertaken between December 2009 and August 2010, at their routine yearly follow-up. Given the phenomenon of the running-in phase in MoM hip replacements, a minimum follow-up of one year was also chosen for TDR patients. The median follow-up for the TDR patients was 34.5 months (13 to 61). The median follow-up for patients with a hip replacement was exactly 12 months, as they had all been recalled for blood samples one year after implantation as part of the study protocol.

Regional ethics committee approval had been granted for the study of all the hip patients but no approval was required for the TDR patients, as the evaluation was considered part of their routine care. Informed consent was still obtained in all cases.

Study population

A total of ten patients with a single-level TDR, 36 with a unilateral hip resurfacing and 21 with a unilateral THA were included in the study and were tested for cobalt and chromium ion levels in whole blood and serum. The pre-operative baseline metal ion levels of 81 patients in the hip replacement trials were used as controls. The number of control patients exceeds the sum of the patients with a hip resurfacing or THA, as only hip replacement patients with a follow-up of at least one year were included. None of these had been exposed to cobalt or chromium, either environmentally or medically, according to a standardised screening questionnaire.

All patients who underwent a TDR had suffered from discogenic back pain that failed to respond to conservative treatment over a period of at least 12 months; they had single-level disc degeneration on MRI; no spondylolisthesis or congenital abnormality; a body mass index (BMI) < 30; no previous back operations; and were aged between 25 and 55 years. Failed conservative treatment included antiinflammatory drugs, physiotherapy, pain treatment and modification of activity.

Maverick TDR plates come in small, medium and large sizes and vary in height between 9 mm and 14 mm. None of the patients included in this study had a small implant, three had a medium implant and seven a large implant; their median height was 10 mm (9 to 11). The TDR was at L4-5 in eight cases and at L5-S1 in two. Additional demographic data are summarised in Table I.

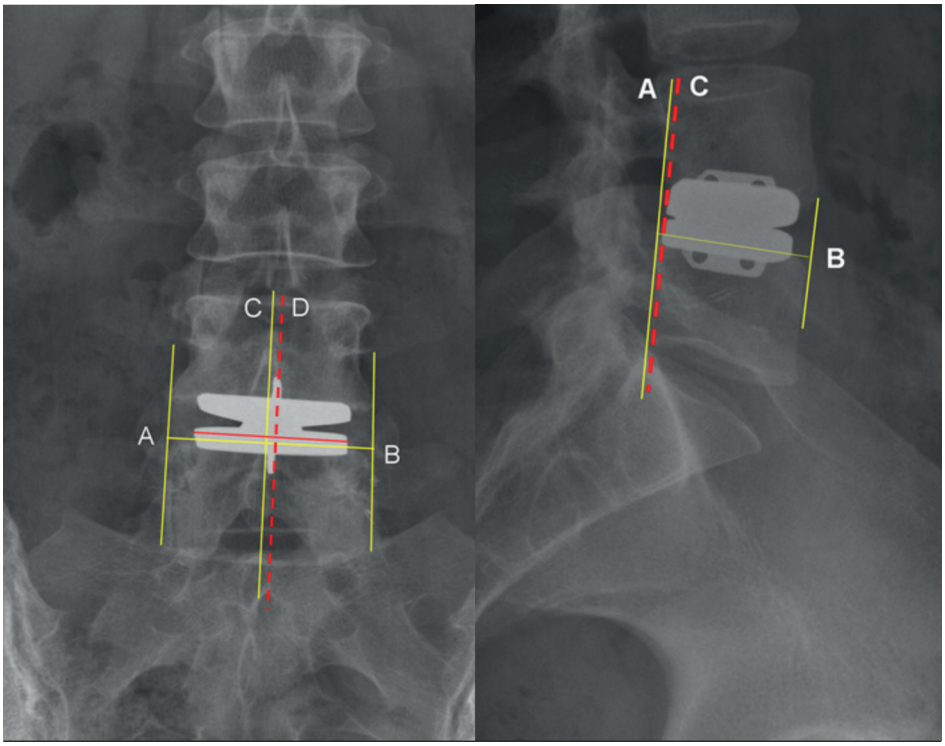


Figure 1. Anteroposterior (left) and lateral (right) radiographs showing a Maverick metal-on-metal total disc replacement, with a ball-and-socket articulation.

The percentage deviation of the prosthesis from the midline of the vertebral body on the anteroposterior view was defined as the difference between the midline of the body (yellow line C) and the midline of the prosthesis (dotted red line D) divided by the distance between points A and B. On the lateral view an adequate position was defined as implant position within 5 mm of the posterior boundary of the endplate (distance between lines A and C).

Clinical scoring, TDR positioning and TDR range of movement

A visual analogue scale (VAS)[25] for low back pain and an Oswestry Disability Index (ODI)[26] were obtained pre-operatively and at regular intervals post-operatively in the TDR group. The range of movement of the TDR was also routinely measured by an author (DJZ): this was defined as the angle between the caudal endplate of the upper vertebral body and the

cranial endplate of the lower vertebral body in the sagittal plane on conventional flexion-extension radiographs.

Because malpositioning of the implant is known to elevate metal ion levels after THA,[27,28] satisfactory placement of each TDR was confirmed on anteroposterior (AP) and lateral radiographs. On the AP view the centre of the implant was compared with the midline of the vertebrae and any deviation was expressed as a percentage of the width of the superior endplate of the inferior vertebra (Figure 1). Central positioning with < 5% deviation was considered satisfactory. On the lateral view, a satisfactory position was registered if the implant was sited within 5 mm of the posterior border of the endplate.

Blood collection

Blood samples were collected in three metal-free vacutainers, a 6 ml BD 'EDTA' and a 5 ml BD 'SST II Advance' system (both Becton Dickinson, Franklin Lakes, New Jersey). The first 5 ml were discarded to eliminate any form of metal contamination from the needle. After blood collection the tube with clot activator was set to rest for at least 30 minutes and was then centrifuged at 3600 rpm for ten minutes. Both tubes were stored at 2°C to 8°C and forwarded to the Laboratory of Toxicology at the University Hospital, Ghent, Belgium, for analysis. The metal ion levels were determined using an inductively-coupled plasma mass spectrometer (ICP-MS) on a Perkin Elmer Elan DRC-e equipped with a standard cross-flow nebuliser and a dynamic reaction cell (Perkin Elmer SCIEX Instruments, Ontario, Canada). Results were quantitatively reported if concentrations exceeded the detection threshold of 0.5 µg/l; all values below the detection limit were registered as 0.1 µg/l for statistical analysis.

Statistical analysis

The data were processed using SPSS 15.0 (SPSS Inc., Chicago, Illinois) and analysed for statistical differences. Variables were controlled for their normal distribution with the Kolmogorov-Smirnov test. A value of < 0.05 was defined as an absence of normal distribution. Median, range and non-parametric tests (Mann-Whitney U, Wilcoxon signed-rank and Kruskal-Wallis tests) were used for all parameters owing to the absence of normal distribution and the small number of patients in the TDR group. Pearson's chi-squared test was used for categorical variables (gender). Statistical significance was defined as a p-value < 0.05.

RESULTS

The characteristics of all implant subgroups are presented in Table I. The clinical scores, range of movement and metal ion levels of each of the TDR patients are shown in Table II. The VAS for low back pain and the ODI both improved significantly after surgery (both $p = 0.005$, Wilcoxon signed-rank test). At the latest follow-up the VAS pain score had decreased by a median of seven points out of ten (4 to 8) against pre-operative levels. The ODI revealed an median post-operative decrease of 39% (24% to 80%).

All TDRs remained mobile at the median follow-up of 34.5 months (Table II) when the median range of movement was 15.5° (10° to 22°).

Regarding the position of the implants, the median deviation of the centre of the TDR from the midline of the vertebra was 2.4% (0% to 4.8%) on the AP view. On the lateral view all TDRs were placed within 5 mm of the posterior border of the adjacent endplate. Accordingly, all ten TDRs could be classified as being appropriately sited on both AP and lateral views.

Cobalt and chromium levels in whole blood and serum

The median cobalt and chromium levels in whole blood and serum for each subgroup of implants are given in Table III and the relationship between them is shown in Figure 2.

TDR versus THA and hip resurfacing

Cobalt and chromium levels in whole blood and serum were significantly lower in the TDR group than in both the hip resurfacing and the THA groups, particularly in the hip resurfacing group ($p < 0.001$, Mann-Whitney U test; Table III). The difference between the THA subgroup and the TDR patients was less pronounced, but with significantly higher cobalt levels in both whole blood and serum and chromium levels in serum for the THA group ($p = 0.004$, $p = 0.007$ and $p = 0.008$, respectively, Mann-Whitney U test). Chromium levels in whole blood were also relatively high in the THA group, but this difference was not statistically significant ($p = 0.053$, Mann-Whitney U test).

Table II. Clinical scores, range of movement and metal ion levels (Co, cobalt; Cr, chromium) in the total disc replacement (TDR) group

Patient number	Level	Follow-up (months)	VAS* (0 to 10)		ODI† (0 to 100)		ROM‡ (°)	Co blood (μg/l)	Co serum (μg/l)	Cr blood (μg/l)	Cr serum (μg/l)
			Pre**	Post**	Pre**	Post**					
1	L4/L5	13	4	0	40	0	17	0.6	0.1	0.1	0.1
2	L4/L5	15	8	2	24	0	15	1.1	0.1	0.1	0.1
3	L4/L5	24	8	0	40	2	12	0.1	0.1	0.1	0.1
4	L4/L5	29	8	1	46	10	16	0.7	0.5	0.1	0.1
5	L4/L5	31	7	0	40	0	12	0.7	0.1	0.1	0.1
6	L4/L5	38	8	4	68	30	17	0.6	0.1	0.1	0.1
7	L4/L5	60	7	0	30	0	22	0.1	0.1	0.1	0.1
8	L4/L5	61	7	0	54	0	21	0.6	0.1	0.1	0.1
9	L5/S1	59	8	0	80	0	10	0.1	0.1	0.1	0.1
10	L5/S1	60	8	2	56	2	10	1.2	1.1	1.1	0.9
Median (range)		34.5 (13 to 61)	8 (4 to 8)	0 (0 to 4)	43 (24 to 80)	0 (0 to 30)	15.5 (10 to 22)	0.6 (0.1 to 1.2)	0.1 (0.1 to 1.1)	0.1 (0.1 to 1.1)	0.1 (0.1 to 0.9)

* VAS, visual analogue scale for pain
† ODI, Oswestry Disability Index
‡ ROM, range of movement in the sagittal plane
** pre- and post-operative

Table III. Median metal ion levels in µg/l (range) in the different prosthesis groups (TDR, total disc replacement; THA, total hip replacement)

	Control (n = 81)	TDR (n = 10)	Hip resurfacing (n = 36)	p-value*	THA (n = 21)	p-value†
Cobalt whole blood	0.1 (0.1 to 0.8)	0.6 (0.1 to 1.2)	1.3 (0.6 to 11.5)	< 0.001	1.1 (0.1 to 2.2)	0.004
Cobalt serum	0.1 (0.1 to 2.6)	0.1 (0.1 to 1.1)	1.1 (0.1 to 7.7)	< 0.001	0.8 (0.1 to 1.9)	0.007
Chromium whole blood	0.1 (0.1 to 1.2)	0.1 (0.1 to 1.1)	1.0 (0.1 to 6.0)	< 0.001	0.5 (0.1 to 1.9)	0.053
Chromium serum	0.1 (0.1 to 2.9)	0.2 (0.1 to 0.9)	1.8 (0.1 to 10.2)	< 0.001	0.9 (0.1 to 2.9)	0.008

* comparison between TDR and hip resurfacing (Mann-Whitney U test),
† comparison between TDR and THA (Mann-Whitney U test)

TDR versus control

Compared with the metal ion levels in the control group, the cobalt and chromium ion levels in whole blood and serum were all significantly higher ($p < 0.001$, Mann-Whitney U test) after both hip resurfacing and THA. For the TDR patients, however, the cobalt levels in serum and the chromium levels in both whole blood and serum did not differ statistically from those in the control group (Figure 2). The only metal trace that appeared to be significantly higher after TDR was cobalt in whole blood ($p < 0.001$, Mann-Whitney U test).

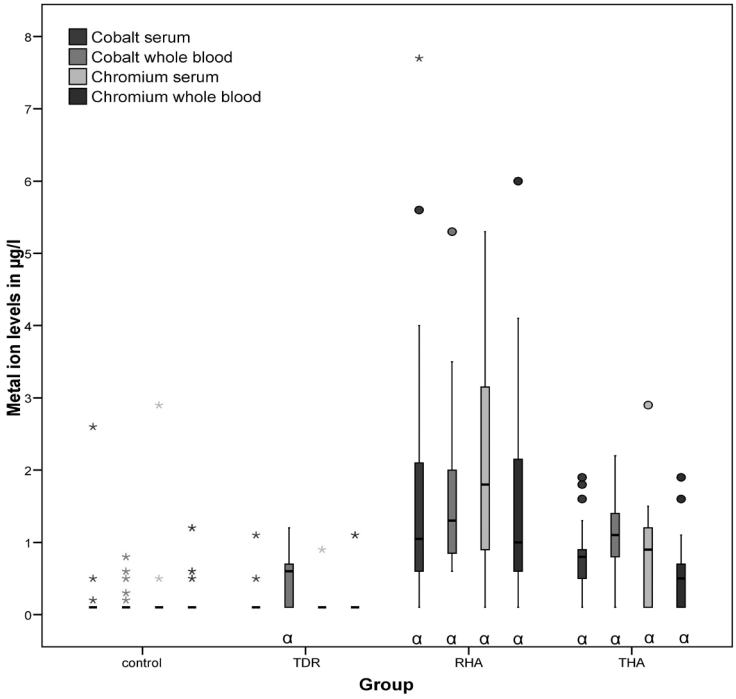


Figure 2. Box plot showing the cobalt and chromium metal ion levels in the total disc replacement (TDR) group in proportion to the other prostheses and the control group.

The horizontal thick black line represents the median, the shaded area the interquartile range and the whiskers the minimum and maximum values. The remainder are outliers (circles) and extreme outliers (asterisks). The 'α' under the whiskers indicates a statistical difference (all $p < 0.001$, Mann-Whitney U test) in metal ion level compared with the control group. Two extreme outliers in the hip resurfacing group lie outside the range displayed: cobalt whole blood at 11.5 µg/l and chromium serum at 10.2 µg/l (THA, total hip replacement).

DISCUSSION

In this study, patients with a well-functioning single-level TDR appeared to have cobalt and chromium levels that were in most cases similar to those measured preoperatively in control patients without any form of MoM implant. Only cobalt levels in whole blood showed a significant median increase (to 0.6 µg/l) after a TDR; this is just above the detection limit of 0.5 µg/l. Metal ion levels in the TDR group were also significantly lower than those after

hip resurfacing or THA, particularly after hip resurfacing. These results are at odds with those of the two other single-centre studies in the literature.[20,21] In these studies of mono- and bisegmental TDR the authors reported a median cobalt serum level of 4.97 µg/l and a chromium serum level of 1.78 µg/l at a median follow-up of 14.8 months. At 36.7 months these median values of cobalt decreased to 1.64 µg/l and chromium increased to 2.50 µg/l, respectively.[21] These figures are much higher than we found in our study, where serum levels of both cobalt and chromium remained below the detection limit at a median follow-up of 34.5 months. Cobalt levels of 4.97 µg/l should cause concern, as they approach levels of toxicity equivalent to the 'exposure equivalent of carcinogenic substances' (EKA values)[29] for industrial workers and the references of the Mayo Medical Laboratories interpretive handbook.[30] In these references, the upper limit of cobalt is defined at 5 µg/l in whole blood. In addition to these reference values, De Smet et al[6] analysed metal ion levels in patients with well- and poorly functioning hip resurfacings and proposed that serum cobalt and chromium levels of 4.4 µg/l (odds ratio (OR) for revision 6.0) and 5.1 µg/l (OR for revision 4.3), respectively, should be the upper limits of acceptability.

We do not have a clear explanation for the differences in metal ion levels found between our study and the earlier studies of Zeh et al.[20,21] Both were performed on patients with the same type of TDR (Maverick TDR). In the studies of Zeh et al,[20,21] patients with both single- and two-level TDRs were included, whereas we only included patients with a single-level replacement. However, the previous studies state that there was no statistically significant difference in metal ion levels after TDR at one or two levels.[20,21]

From the literature on hip replacement we know that an optimal implant position is mandatory to ensure low friction and subsequently low metal ion levels.[27] Adequate positioning of the TDR is also a prerequisite for normal spine kinematics,[1,2,31] and it seems reasonable to assume that appropriate positioning of the TDR has an influence on low metal ion release as it does for hip replacement.

The range of movement of the device may also influence the amount of metal ion release, as loss of movement would inevitably lead to a decrease in wear. All TDRs appeared to have maintained a substantial range of movement on flexion-extension radiographs, with a median of 15.5° (10° to 22°) at final follow-up. Therefore we can conclude that the low metal ion levels cannot simply be explained by an absence of movement of the implants. No information on implant position and range of movement is given in the studies of Zeh et al.[20,21]

The differences we found are probably related to differences in the protocols we used for blood collection and processing. Adequate and reliable measurement of ultra-low levels of metal ions is a delicate process and vulnerable to potential contamination, such as traces of metal from the needle. In our protocol the first 5 ml of blood were discarded to avoid potential contamination. In addition, we used ICP-MS on a Perkin Elmer Elan DRC-e equipped with a standard cross-flow nebuliser and a dynamic reaction cell (Perkin Elmer SCIEX), which is currently considered the optimal processing technique.[32]

Another advantage of our study is that we were able to correlate the metal ion levels found after TDR with control levels and levels after hip resurfacing and THA. Samples from all these subgroups were evaluated at the same laboratory using the same rigid protocol.

In our study both cobalt and chromium levels in the TDR group were significantly lower than after THA ($p = 0.053$) and hip resurfacing ($p < 0.001$). Given the current concern about the serious adverse events that have occurred after MoM hip replacements, and in particular after hip resurfacing, this is an important finding. We conclude that the chances of a significant increase in metal ion levels in both whole blood and serum after TDR are substantially lower than after THA or hip resurfacing. Apparently the amount of wear debris from a well-positioned TDR is relatively low. This corresponds with an earlier study where wear debris from a Maverick TDR was estimated to be between 0.38 mm^3 and 0.44 mm^3 per year, compared with 1 mm^3 to 5 mm^3 for a MoM hip replacement.[9,33] This difference in wear is almost certainly due to the fact that the kinematics of a TDR, such as loading, shear forces, contact area and range of movement, are profoundly different from those of any hip replacement. The range of movement in a TDR is relatively limited and the shear forces are rather low, owing to the contained position of the device. This will result in lower friction of the articulating surfaces and reduced wear.

There are limitations to our study. No pre-operative metal ion levels were assessed in the TDR group, which made it impossible to determine the actual increase in metal ion levels after surgery. As cobalt levels in serum and chromium levels in both whole blood and serum remained generally below the detection limit of 0.5 µg/l at a median of 34.5 months after a TDR, one can argue whether this limitation is truly relevant. We believe that the available dataset of 81 control patients from an ongoing hip trial provides an appropriate surrogate value.

In addition, it should be noticed that there is a difference in follow-up between the different implant groups. Patients in the TDR group had a longer median follow-up (34.5 months) than the hip resurfacing and THA groups (12 months), but we do not believe that this difference is a major confounding factor, as the metal ion levels of the TDR are certainly beyond their running-in phase and must have stabilised. These levels are also lower than the longterm figures for MoM THA and hip resurfacings given in the literature.[7,8,24]

The TDR group was small. A larger population would, however, probably not have shown any greater difference between the TDR and the control group, as all values were in a limited range and almost always below the limit of detection.

In conclusion, we believe that there is only limited cause for concern, as in this study the post-operative metal ion levels were significantly lower after TDR than after THA and hip resurfacing, and were generally comparable to those in the general population. These findings are more reassuring than those previously published.[20,21] Local soft-tissue necrosis or pseudotumour formation as a result of metal ion debris reaching toxic release levels, as has been described after MoM hip replacement, would seem unlikely to occur after an MoM lumbar TDR. However, the exact pathology of pseudotumour formation is far from fully understood, and as well as a toxic reaction to an abundant volume of metal particles, a delayed hypersensitivity reaction to these particles has also been described as a causative factor.[34] With a hypersensitivity reaction metal ions do not have to be elevated beyond toxic levels in order to cause a soft-tissue reaction. So far, only two case reports are available in the literature after a TDR,[14,16] where the authors describe a soft-tissue mass posterior to the implant encroaching on the spinal cord. Revision surgery was performed and histology showed a lymphocyte-dominated response in the tissue similar to those reported in patients with an MOM hip prosthesis.[13] These case reports and other similar unpublished reports still justify caution when using TDRs. We encourage spinal surgeons using MoM TDR to follow their patients at regular intervals, particularly if they complain of increasing pain, when investigation should include measurement of metal ion levels.

REFERENCES

1. Le Huec JC, Lafage V, Bonnet X, et al. Validated finite element analysis of the maverick total disc prosthesis. *J Spinal Disord Tech* 2010;23:249-57.
2. Tournier C, Aunoble S, Le Huec JC, et al. Total disc arthroplasty: consequences for sagittal balance and lumbar spine movement. *Eur Spine J* 2007;16:411-21.
3. Huang RC, Tropiano P, Marnay T, et al. Range of motion and adjacent level degeneration after lumbar total disc replacement. *Spine J* 2006;6:242-7.
4. Doorn PF, Campbell PA, Worrall J, et al. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res* 1998;42:103-11.
5. Sieber HP, Rieker CB, Köttig P. Analysis of 118 second-generation metal-on-metal retrieved hip implants. *J Bone Joint Surg [Br]* 1999;81-B:46-50.
6. DeSmet KA, Campbell PA, Van Orsouw M, Gill HS. Interpretation of metal ion levels after metal-on-metal resurfacing. *Procs AAOS* 2010; Poster: P100.
7. Lazennec JY, Boyer P, Poupon J, et al. Outcome and serum ion determination up to 11 years after implantation of a cemented metal-on-metal hip prosthesis. *Acta Orthop* 2009;80:168-73.
8. Daniel J, Ziaee H, Pradhan C, McMinn DJ. Six-year results of a prospective study of metal ion levels in young patients with metal-on-metal hip resurfacings. *J Bone Joint Surg [Br]* 2009;91-B:176-9.
9. Amstutz HC, Campbell P, McKellop H, et al. Metal on metal total hip replacement workshop consensus document. *Clin Orthop* 1996;329(Suppl):297-303.
10. Haddad FS, Thakrar RR, Hart AJ, et al. Metal-on-metal bearings: the evidence so far. *J Bone Joint Surg [Br]* 2011;93-B:572-9.
11. Vendittoli PA, Roy A, Mottard S, et al. Metal ion release from bearing wear and corrosion with 28 mm and large-diameter metal-on metal bearing articulations: a follow-up study. *J Bone Joint Surg [Br]* 2010;92-B:12-19.
12. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. *J Biomed Mater Res* 2001;56:427-36.

13. Willert HG, Buchhorn GH, Fayyazi A, et al. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints: a clinical and histomorphological study. *J Bone Joint Surg [Am]* 2005;87-A:28-36.
14. Cavanaugh DA, Nunley PD, Kerr EJ 3rd, Werner DJ, Jawahar A. Delayed hyperreactivity to metal ions after cervical disc arthroplasty: a case report and literature review. *Spine* 2009;34:E262-5.
15. Park YS, Moon YW, Lim SJ, et al. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg [Am]* 2005;87-A:1515-21.
16. Berry MR, Peterson BG, Alander DH. A granulomatous mass surrounding a Maverick total disc replacement causing iliac vein occlusion and spinal stenosis: a case report. *J Bone Joint Surg [Am]* 2010;92-A:1242-5.
17. Pandit H, Glyn-Jones S, McLardy-Smith P, et al. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg [Br]* 2008;90-B:847-51.
18. Langton DJ, Jameson SS, Joyce TJ, et al. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: a conseqeunce of excess wear. *J Bone Joint Surg [Br]* 2010;92-B:38-46.
19. No authors listed. Medicines and Healthcare products Regulatory Agency (MHRA). Metal-on-metal (MoM) hip replacements: medical device alert 2010/033, 2010. http:/ /www.mhra.gov.uk (date last accessed 22 March 2011).
20. Zeh A, Planert M, Siegert G, et al. Release of cobalt and chromium ions into the serum following implantation of the metal-on-metal Maverick-type artificial lumbar disc (Medtronic Sofamor Danek). *Spine* 2007;32:348-52.
21. Zeh A, Becker C, Planert M, Lattke P, Wohlrab D. Time-dependent release of cobalt and chromium ions into the serum following implantation of the metal-onmetal Maverick type artificial lumbar disc (Medtronic Sofamor Danek). *Arch Orthop Trauma Surg* 2009;129:741-6.
22. Bisseling P, Smolders JMH, Hol A, van Susante JLC. No clear influence of preference bias on satisfaction and early outcome in resurfacing hip arthroplasty. *Acta Orthop* 2011;82:161-5.
23. Smolders JMH, Hol A, Rijnders T, van Susante JLC. Changes in bone mineral density in the proximal femur after hip resurfacing and uncemented total hip replacement: a prospective randomised controlled study. *J Bone Joint Surg [Br]* 2010;92-B:1509-14.
24. Malviya A, Ramaskandhan J, Holland JP, Lingard EA. Metal-on-metal total hip arthroplasty. *J Bone Joint Surg [Am]* 2010;92-A:1675-83.
25. Huskisson EC. Measurement of pain. *Lancet* 1974;2:1127-31.

26. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980;66:271-3.
27. De Haan R, Pattyn C, Gill HS, et al. Correlation between inclination of the acetabular component and metal ion levels in metal-on-metal hip resurfacing replacement. *J Bone Joint Surg [Br]* 2008;90-B:1291-7.
28. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AV. The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. *J Bone Joint Surg [Br]* 2008;90-B:1143-57.
29. Morgan MS, Schaller KH. An analysis of criteria for biological limit values developed in Germany and in the United States. *Int Arch Occup Environ Health* 1999;72:195-204.
30. No authors listed. Mayo Medical Laboratories. Interpretive handbook, test number 80084: cobalt, serum. http://www.mayomedicallaboratories.com/interpretive-guide/ ?alpha=C&unit_code=80084 (date last accessed 23 March 2011).
31. Schmidt H, Galbusera F, Rohlmann A, Zander T, Wilke HJ. Effect of multilevel lumbar disc arthroplasty on spine kinematics and facet joint loads in flexion and extension: a finite element analysis. *Eur Spine J* 2010;Epub.
32. Bolann BJ, Rahil-Khazen R, Henriksen H, Isrenn R, Ulvik RJ. Evaluation of methods for trace-element determination with emphasis on their usability in the clinical routine laboratory. *Scand J Clin Lab Invest* 2007;67:353-66.
33. Mathews HH, Lehuec JC, Friesem T, Zdeblick T, Eisermann L. Design rationale and biomechanics of Maverick total disc arthroplasty with early clinical results. *Spine J* 2004;4(Suppl):268-75.
34. Pandit H, Vlychou M, Whitwell D, et al. Necrotic granulomatous pseudotumours in bilateral resurfacing hip arthroplasties: evidence for a type IV immune response. *Virchows Arch* 2008;453:529-34.

following implantation of the met
Sofamor Danek). *Spine* 2007;32:348-52.
21. Zeh A, Becker C, Planert M, Lattke P, Wohlra
chromium ions into the serum following implantat
artificial lumbar disc (Medtronic Sofamor Danek). *Arch*
Bisseling P, Smolders JMH, Hol A, van Susante JLC. No c
ction and early outcome in resurfacing hip arthroplas
23. Smol MH, Hol A, Rijnders T, van Susante JLC. Change
proximal fe fter hip resurfacing and uncemented total
randomised conti tudy. *J Bone Joint Surg [Br]* 2010;92-E
24. Malviya A, Ramaskand Holland JP, Lingard EA. Metal
J Bone Joint Surg [Am] 2010; 675-83.
Huskisson EC. Measurement of pa *cet* 1974;2:1127-

CHAPTER 6

Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties

Results of a screening metal artefact reduction sequence-MRI study

P. Bisseling, B. W. K. de Wit, A. M. Hol, M. J. van Gorp, A van Kampen, J. L. C. van Susante

Bone Joint Journal. 2015;97-B:1175–82.

ABSTRACT

Patients from a randomised trial on resurfacing hip arthroplasty (RHA) (n = 36, 19 males; median age 57 years, 24 to 65) comparing a conventional 28-mm metal-on-metal total hip arthroplasty (MoM THA) (n = 28, 17 males; median age 59 years, 37 to 65) and a matched control group of asymptomatic patients with a 32 mm ceramic-on-polyethylene (CoP) THA (n = 33, 18 males; median age 63 years, 38 to 71) were cross-sectionally screened with metal artefact reducing sequence-MRI (MARS-MRI) for pseudotumour formation at a median of 55 months (23 to 72) post-operatively. MRIs were scored by consensus according to three different classification systems for pseudotumour formation.

Clinical scores were available for all patients and metal ion levels for MoM bearing patients.

Periprosthetic lesions with a median volume of 16 ml (1.5 to 35.9) were diagnosed in six patients in the RHA group (17%), one in the MoM THA group (4%) and six in the CoP group (18%). The classification systems revealed no clear differences between the groups. Solid lesions (n = 3) were exclusively encountered in the RHA group. Two patients in the RHA group and one in the MoM THA group underwent a revision for pseudotumour formation. There was no statistically significant relationship between clinical scoring, metal ion levels and periprosthetic lesions in any of the groups.

Periprosthetic fluid collections are seen on MARS-MRI after conventional CoP THA and RHA and may reflect a soft-tissue collection or effusion.

Currently available MRI classification systems seem to score these collections as pseudotumours, causing an overestimatation of the incidence of pseudotumours.

INTRODUCTION

In recent years several studies[1-3] have reported pseudotumour formation after metal-on-metal (MoM) total hip arthroplasty (THA). These studies raised concerns about the hazardous side-effects of these bearings and resulted in official safety alerts and market withdrawal of some designs of resurfacing hip arthroplasty (RHA).[4-6] These alerts included recommendations to screen patients with MoM bearings, using cross-sectional imaging such as ultrasound, CT and MRI. As a consequence, the presence of soft-tissue and fluid collections, muscle atrophy and oedema have been reported in relation to joint arthroplasties, which were not previously seen on conventional imaging.[7-9] These lesions have subsequently also been described in asymptomatic MoM arthroplasties.[1,7,10,11] The incidence of pseudotumour formation varies from 0.1% to 67%, and latterly it has increased.[1-3,9-13] Various classification systems have been introduced to evaluate and quantify these lesions but their ability to differentiate between benign and pathological lesions is unknown.[1,12,14,15] There is no consensus on the true incidence and clinical significance of many of the MRI findings which are generally referred to as pseudotumours.

Studies on the incidence of pseudotumours using CT or MRI in arthroplasties of the hip other than those with MoM bearings are scarce.[2,7] It could be hypothesised that identical periprosthetic lesions might be present on MRI in patients with bearings other than MoM and that these lesions could also be classified as pseudotumours by current classification systems.

Our objective was to determine the incidence of periprosthetic lesions diagnosed by ´metal artefact reducing sequence´-MRI (MARS-MRI) in patients from a closed randomised trial on RHA *versus* a 28-mm MoM THA, and to compare the findings with the incidence of periprosthetic lesions in a matched control group of asymptomatic patients with a ceramic-on-polyethylene (CoP) conventional THA. Periprosthetic lesions were graded by three classification systems for pseudotumour given in literature.

PATIENTS AND METHODS

For this study, all patients included in a closed randomised controlled trial (RCT) comparing RHA (n = 36) with a 28-mm conventional MoM uncemented THA (MoM THA) (n = 28)[16] were cross-sectionally analysed with MARS-MRI during follow-up. These patients were compared with a matched control group of patients with a CoP THA (n = 33).

Patients enrolled in the RCT between June 2007 and April 2010 were randomly assigned by a computer-generated variable block to receive either a RHA or a MoM THA. This study was designed to compare the functional results and metal ion blood levels of patients after RHA *versus* MoM THA. One criterion for inclusion in the RCT was age < 65 years. Further details are given in the previous paper.[16]

As part of this study, all patients included in the RCT who had not undergone revision during the follow-up period were invited to complete questionnaires and undergo MARS-MRI scans. They were matched by computer to asymptomatic patients with a primary CoP THA, without a prior infection, from a database of patients who underwent this procedure between June 2007 and April 2010 in the same hospital. Matching was performed on period of follow-up within a margin of three months and gender using a computer program (Mathlab 2012A, The MathWorks Inc, Natick, Massachusetts).

Of the patients included in the RCT, six had required revision during follow-up. For these patients the prerevision MRI, when available (two of six), was analysed and scored according to an identical protocol by two radiologists (BW, MG) who were blinded to the cause of revision. The operation note of the revision surgery (four of six) was used for patients without an available MRI to determine whether a pseudotumour was considered to be present macroscopically. All revisions were performed by the senior author (JS) with a broad clinical experience in adverse reactions to metal debris. A summary of the inclusion and subsequent follow-up of patients in the RCT is given in the Consolidated Standards of Reporting Trials statement (Figure 1).

Approval from the regional ethics committee from the Radboud University Nijmegen Medical Centre for the RCT was obtained (number LTC 419-071206, Committee Human Research number (CCMO) 2007/015; EudraCT trial register number 2006-005610-120). The original study did not include cross-sectional MRI screening or a matched control group. This was addressed with additional ethical approval (number LTC 939/190713, Committee

Human Research number NL 44703.091.13, registration number 2013/221). All patients provided informed consent. This study was performed in compliance with the Helsinki Declaration of 2008.[17]

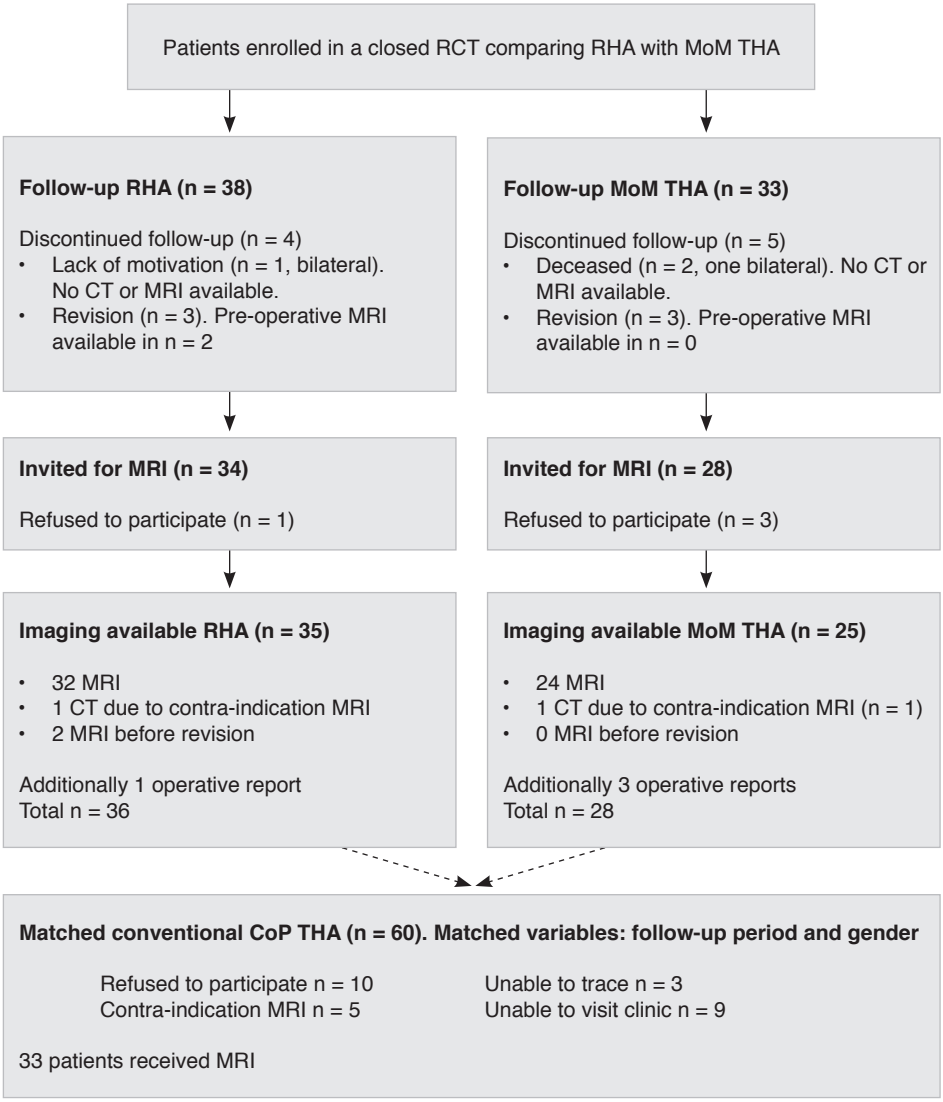


Figure 1. Consolidated Standards of Reporting Trials statement.

RCT, randomised controlled trial; RHA, resurfacing hip arthroplasty; MoM, metal-on-metal; CoP, ceramic-on-polyethylene; THA, total hip arthroplasty.

All operations were performed through a posterolateral approach by an experienced surgeon (JS) who undertook > 100 THAs annually. The surgical details have been described previously.[16] In the RHA group, a cobalt-chromium (CoCr) alloy RHA was implanted (Conserve Plus; Wright Medical Technology, Arlington, Tennessee) with a median femoral head diameter of 49 mm (42 to 54). In the MoM THA group, an uncemented tapered stem and a threaded titanium acetabular shell with a polyethylene insert and an integral metal liner was implanted (Zweymuller Alloclassic stem and Zweymuller Alloclassic CSF cup; Zimmer Orthopaedics, Warsaw, Indiana) together with a metal (CoCr) 28-mm head (Metasul; Zimmer Orthopaedics). The CoP THA group received an identical femoral component and acetabular shell but the latter was lined with a polyethylene insert and articulated with a ceramic 32-mm modular head (Biolox Delta, Zimmer Orthopaedics). All groups received identical antibiotic, thrombosis prophylaxis and rehabilitation programmes.

Imaging studies were performed using a 1.5-T MR scanner (Philips, Best, Netherlands) and a 16-channel body coil. A standard MARS protocol was used with four sequences, transverse T1-weighted images, transverse T2-weighted images, coronal short tau inversion recovery images and coronal T2-weighted images.

MRI was contraindicated in two patients. One in the RHA group had a neurostimulation device and one in the MoM THA group had a cochlear implant. These patients underwent CT scanning with a standard protocol on a 40-slice CT scanner (Brillance 40, Philips, Best, The Netherlands).

MRI and CT scans were interpreted by consensus between a musculoskeletal radiologist (MG) with ten years of experience and a radiologist with three years of experience (BW), both blinded to patient data and symptoms. Periprosthetic lesions were scored according to three classification systems; the Anderson score,[12] the system of Hart et al[1] and a system described by Boomsma et al[13] (Table I). Lesions were considered to be a pseudotumour if the criteria of at least one of these systems was met: an Anderson score 'C',[12] a Boomsma grade > III[13] and every lesion that satisfied the criteria of Hart et al.[1] The volume of the pseudotumour was calculated using post-processing software in our Picture Archive Communication System (Sectra, Linköping, Sweden) by outlining the circumference of the lesion on each slice. The inclination angle of the acetabular component was measured with reference to the inter-teardrop line on standardised anteroposterior pelvic radiographs.

All patients completed a Short Form-12 (SF-12), Oxford hip score questionnaire and a visual analogue scale (VAS) satisfaction score of 0 to 100 (worst to best). The Harris hip score[18] and the University of California at Los Angeles activity scale[19] were assessed by two members of the research staff (AH, PB) who collected and registered all the forms at the time of the MARS-MRI. Identical clinical outcome measurements were available pre-operatively and at six, 12, 24, 36 and 60 months for patients enrolled in the RCT. The latest available scores were used in those patients who underwent revision during follow-up.

CoCr serum levels were available for the patients enrolled in the RCT, including the latest metal ion levels of all patients who underwent revision during follow-up. Blood samples were collected pre-operatively and at three, six, 12, 24, 36 and 60 months post-operatively. The latest available metal ion level was used. Samples were collected according to a strict protocol to eliminate any form of metal contamination and analysis was undertaken using an inductively-coupled plasma mass spectrometer. The details have been reported previously.[16] The results were quantitatively reported if concentrations exceeded the detection threshold of 0.5 µg/l. All values below the limit of detection were registered as 0.1 µg/l for the purposes of statistical analysis.

Statistical analysis

The variables were tested for normal distribution using the Shapiro–Wilk test. Owing to a relatively small number of patients and an even smaller number of those with a pseudotumour, none of the variables had a normal distribution. Therefore, the median and range were used for all variables and non-parametric tests were used. Differences between two groups were determined by the Mann–Whitney U test and the Kruskal–Wallis test for analysis of more than two groups. A sub-analysis was performed on the relation between periprosthetic lesions on MRI and clinical scores. For this sub-analysis, the whole study population was split into a group with lesions graded as 'pseudotumour' by one of the classification systems and those without a periprosthetic lesion. Secondly, the same relationship was analysed for each type of arthroplasty separately. Differences were considered statistically significant with a p-value < 0.05. IBM-SPSS Statistics version 20.0 (IBM Corp., Armonk, New York) was used for statistical analysis. No power analysis was performed owing to the fact that the number of patients included in the RCT determined the total number of patients.

Table I. Used classification systems by Anderson et al[12], Hart et al[1] and Boomsma et al[13]

Grade	Description	Criteria
Anderson et al grading system		
A	Normal or acceptable	Normal post-operative appearances including seromas and small hematomas
B	Infection	Fluid-filled cavity with high signal T2 wall; inflammatory changes in soft-tissue; ± bone marrow oedema
C1	Mild MoM disease	Periprosthetic soft-tissue mass with no hyperintense T2W fluid signal or fluidfilled peri-prosthetic cavity; either less than 5 cm maximum diameter.
C2	Moderate MoM disease	Peri-prosthetic soft-tissue mass/fluid-filled cavity greater than 5 cm diameter or C1 lesion with either of following: (1) muscle atrophy or oedema in any muscle other than short external rotators or (2) bone marrow oedema: hyperintense on STIR
C3	Severe MoM disease	Any one of the following: (1) fluid-filled cavity extending through deep fasci, (2) a tendon avulsion, (3) intermediate T1W soft-tissue cortical or marrow signal, (4) fracture
Hart et al grading system		
1	Thin-walled	Content: Fluid-like; hypointense on T1,hyperintense on T2. Shape: flat, with walls mainly in apposition
2a	Thick-walled or irregular	Content: Fluid-like: hypointense on T1,hyperintense on T2. Shape: not flat, with > 50% of the walls not in apposition
2b	Thick-walled or irregular	Content: atypical fluid: hyperintense on T1, variable on T2. Shape: any shape
3	Solid throughout	Content: mixed signal. Shape: any shape
Boomsma grading system		
I	Normal or acceptable	Thickening of capsule up to 4 mm to 6 mm
II	Reactive	Thickening of capsule of > 6 mm, but not more than the neck of the prosthesis, with or without bulging and without eccentric enlargement with respect to the capsule
III	Mild MoM disease	Consists of a bulging capsule both anteriorly and posteriorly
IV	Moderate MoM disease	Represents eccentric bulging or enlargement of the capsule, which is often seen inferomedially to the prosthetic head
V	Severe MoM disease	Represents the so-called bursitis mimicker, often extending posterolaterally with extensive filling of the subtrochanteric bursa, or anteriorly by filling of the iliopectineal bursa, which can extend into the abdominal compartment

MoM, metal-on-metal; STIR, short tau inversion recovery

RESULTS

The demographic data are summarised in Table II. Patients in the CoP THA group were significantly older than those in the RCT (p = 0.001, Kuskal–Wallis test).

Lesions classified as 'pseudotumour' or 'MoM disease' by any of the three MRI scoring systems were seen in six patients in the RHA group (17%), in one in the MoM THA group (4%) and in six in the CoP THA group (18%) (Figure 2). These differences were not statistically significant (p = 0.19, Kruskal–Wallis test). From the relatively small number of patients in each group, the statistical power of these findings is, however, limited. For that reason detailed information on all patients with a periprosthetic lesion, including clinical scores, acetabular component inclination, metal ion levels and the grading of the three MRI classification systems, is given in Table III.

Generally there were no differences in the grade of periprosthetic lesions between the three groups, as is shown in Table III. Relatively high grade 'pseudotumours' were encountered irrespective of the group and classification system. Two patients had a lesion that was not scored as a 'pseudotumour' or 'MoM disease' by all three classification systems. One patient in the RHA group and one in the CoP THA group was classified as having a Boomsma grade II lesion,[13] which represented a reactive lesion. Solid lesions (n = 3) graded as a Hart et al[1] grade 3, were exclusively seen in the RHA group.

The median volume of the lesions was 16 ml (1.5 to 35.9) with no statistical difference in volume between groups (p = 0.2, Kruskal-Wallis test). Lesions were seen in nine men and four women, but this gender difference was not significant (p = 0.29, Mann-Whitney U test). The median inclination angle of the acetabular component of patients with a lesion was 44° (33° to 57°). Again no significant difference in this angle could be established between patients with or without a lesion on MRI (p = 0.20, Mann- Whitney U test).

Overall good clinical scores were seen without significant differences between the three groups (Table II). The only significant difference was in the median VAS satisfaction scores; this was significantly lower for the MoM THA group with a score of 85 (18 to 100) compared with 91 (0 to 100) and 95 (23 to 100) for the RHA and CoP THA groups respectively (p = 0.045, Kruskal–Wallis test). More detailed information on the clinical scores at different time intervals for the patients in the RCT has previously been reported.[16]

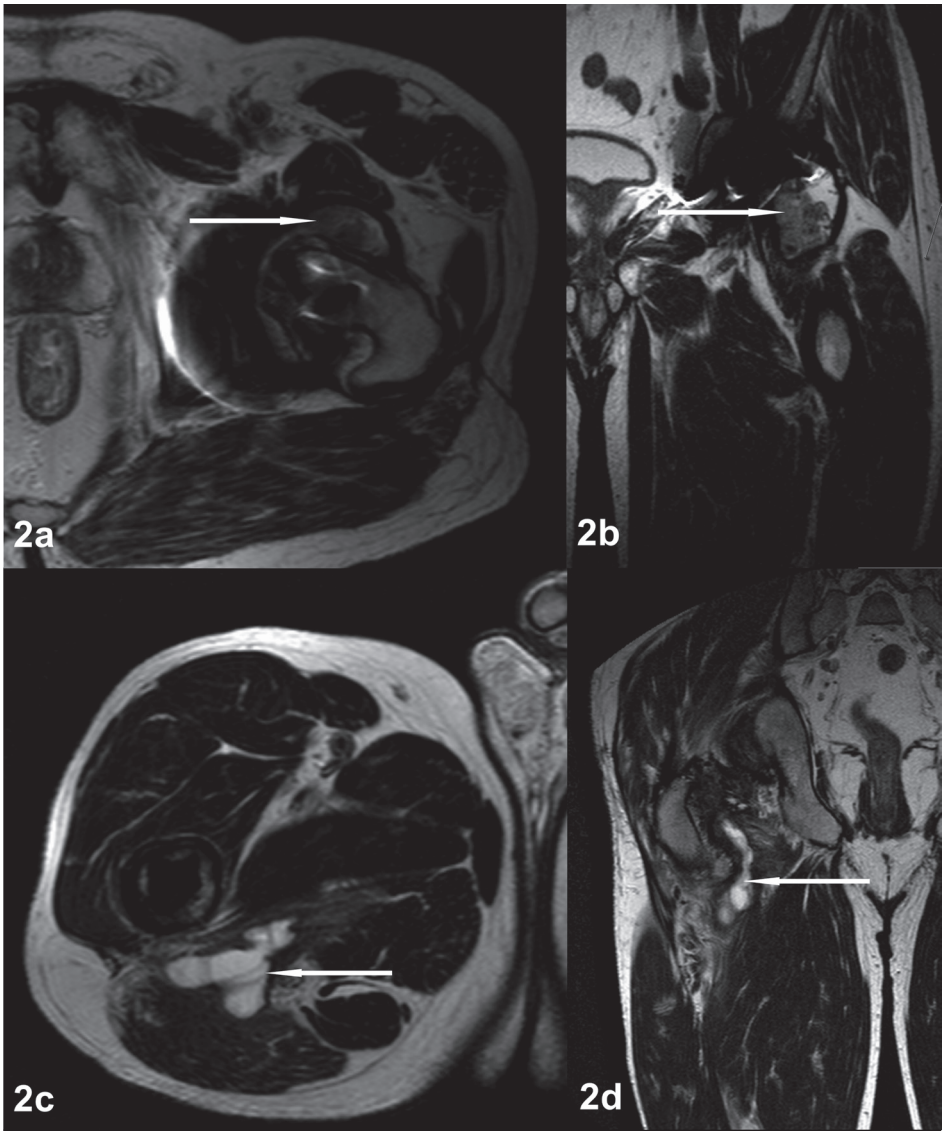


Figure 2. MRIs showing the compilation of typical lesions (indicated by arrow) graded as pseudotumour on the selected classification systems.

Images a) and b) show a resurfacing hip arthroplasty graded Anderson C2, Hart 3 and Boomsma IV; and images c) and d) show a ceramic-on-polyethylene total hip arthroplasty graded Anderson C3, Hart 2a and Boomsma V.

No statistically significant difference was encountered between the clinical scores and characteristics of the periprosthetic lesions overall ($p \geq 0.13$, Mann–Whitney U test) and in the different prosthesis groups separately ($p \geq 0.07$, Mann– Whitney U test). However, it is acknowledged that the groups are relatively small for statistical sub-analysis.

Revision because of a destructive pseudotumour occurred in two patients in the RHA group (5%) and in one in the MoM THA group (3%); all three at 36 months postoperatively. The remaining revisions were related to osteonecrosis of the femoral head in one patient in the RHA group and two with recurrent dislocation in the MoM THA group. MRI scans before revision for pseudotumour formation were available in both patients in the RHA group and were used for retrospective grading. Of the remaining four patients with a revision, one large destructive pseudotumour in a MoM THA patient was described in the operation notes as an unanticipated finding. This was the only pseudotumour encountered in the MoM THA group.

Median serum cobalt levels, including the levels in the six patients who underwent a revision for RHA and MoM THA, after a median of 55 months (36 to 72) and 56 months (23 to 69) were 1.3 ng/mL (0.1 to 22.1) and 0.8 ng/ mL (0.1 to 2.4), respectively. In contrast to cobalt, the difference in median serum levels of chromium was significant with 1.8 (0.1 to 29.9) for the RHA group and 0.5 (0.1 to 2.6) for the MoM THA group ($p < 0.001$). No statistically significant difference was encountered between metal ion levels in patients with periprosthetic lesions and those without (Cobalt $p = 0.06$; Chromium $p = 0.068$, Mann–Whitney U test).

Table II. Demographic data presented as medians with ranges RHA.

	RHA (n=36)	THA MoM (n=28)	THA CoP (n=33)	p-value
Gender (males)	19	17	18	0.809
Age* (yrs)	57 (24.1 to 64.8)	59 (37.0 to 64.7)	63 (38.6 to 70.5)	0.001
Follow-up (mths)	55 (36 to 72)	56 (23 to 69)	54 (40 to 72)	0.861
Pseudotumour	6	1	6	0.194
HHS	98 (62 to 100)	100 (59 to 100)	97 (64 to 100)	0.616
OHS	14 (12 to 34)	14 (12 to 43)	13 (12 to 27)	0.426
VAS satisfaction*	91 (0 to 100)	85 (18 to 100)	95 (23 to 100)	0.045
UCLA	8 (3 to 10)	7 (4 to 10)	7 (4 to 10)	0.294
SF-12 physical component	100 (0 to 100)	100 (25 to 100)	75 (0 to 100)	0.244
SF-12 mental component	80 (50 to 100)	80 (30 to 100)	80 (40 to 100)	0.850
Cobalt serum (ng/L)	1.3 (0.1 to 22.10)	0.8 (0.1 to 2.4)	NA	0.087
Chromium serum † (ng/L)	1.8 (0.1 to 29.9)	0.5 (0.1 to 2.6)	NA	<0.001
Cup angle (°)	45 (30 to 62)	48 (31 to 62)	46 (31 to 60)	0.223

resurfacing hip arthroplasty;
THA, total hip arthroplasty;
MoM, metal-on-metal;
CoP, ceramic-on-polyethylene;
HHS, Harris hip score;
OHS, Oxford hip score;
VAS, visual analogue scale;
UCLA, University of California at Los Angeles;
SF-12, Short-Form 12;
NA, not applicable
† Significant difference between the groups, Mann–Whitney U test
* Significant difference between the groups, Kruskal–Wallis test

Table III. Clinical scores, metal ion levels, volume and MRI grading of the patients diagnosed with a pseudotumor.

	Prosthesis	Imaging	Pseudotumor characteristics	Cup angle	HHS	Oxford	ULCA	Co serum	Cr serum	volume	Anderson score	Hart score	Boomsma
1	RHA†	MRI	Mixed fluid and solid. Bulging of the capsule anteriorly and posteriorly.	37.5	91	16	7	2.0	3.0	23.7 ml	C2	3	IV
2	RHA	MRI	Fluid filled. Bulging of the capsule and extension in the m. pectineus.	34.8	94	16	7	2.9	3.0	26.4 ml	C3	2a	V
3	RHA	MRI	Fluid filled. Bulging of the capsule anteriorly and posteriorly	42.7	100	13	10	0.9	1.9	10,6 ml	C1	2a	III
4	RHA	MRI	Fluid filled. within normal anatomic boundaries of the capsule with focal bulging of the posterolateral capsule.	43	96	15	9	1.5	2.2	24,9 ml	C1	2a	IV
5	RHA	MRI	Mixed fluid and solid. Anterior bulging	49.4	100	13	10	0.6	0.1	12,0 ml	C1	3	II
6	RHA†	MRI	Mixed fluid and solid. Bulging of the capsule anteriorly and posteriorly and eccentric bulging posterolateraly.	32.8	78	25	8	21.2	16.0	n.a.	C2	3	IV
7	MoM THP†	report	Milky-like fluid from bursa. Intra-operative frozen section and cultures revealed no infection.	51.2	59	43	4	1.6	1.3	n.a.	n.a.	n.a.	n.a.
8	THP	MRI	Fluid filled. No bulging of the capsule.	42.5	96	12	9	n.a.	n.a.	1,5 ml	C1	1/2a	II
9	THP	MRI	Fluid filled. Bulging of the capsule and focal extension into the adductors.	44.1	90	16	9	n.a.	n.a.	35,9 ml	C3	2a	V
10	THP	MRI	Fluid filled. Eccentric bulging of the posterolateral capsule.	46.1	96	20	6	n.a.	n.a.	14,3 ml	C2	2a	IV
11	THP	MRI	Fluid filled. Bulging of the poserolateral capsule into the trochanteric bursa.	45.7	100	12	10	n.a.	n.a.	11,7 ml	C2	2a	V
12	THP	MRI	Fluid filled. bulging of the poserolateral capsule into the trochanteric bursa.	56.5	98	13	7	n.a.	n.a.	6,4 ml	C2	2a	V
13	THP	MRI	Fluid filled. Bulging of the capsule anteriorly and posteriorly.	48.7	98	13	7	n.a.	n.a.	7,9 ml	C2	2a	III

† Revision during follow-up

DISCUSSION

This study illustrates that periprosthetic lesions seen on MARS-MRI and classified as 'pseudotumours' by currently available scoring systems, are not exclusively seen in MoM hip arthroplasties. We found the incidence of periprosthetic lesions to be equally distributed between the RHA (17%) and CoP THA (18%) groups, whereas these lesions were less commonly identified in the MoM THA group (4%). Solid periprosthetic lesions were exclusively seen in the RHA group, while all other lesions were bulging periprosthetic fluid collections. Nevertheless, the three classification systems graded most lesions as a 'pseudotumour' or 'MoM disease'.

In recent years, numerous cross-sectional studies have described solid masses and fluid collections in patients with MoM implants. The masses and fluid collections were mainly classified as adverse reaction to metal debris, pseudotumour or MoM disease and have been reported in symptomatic and asymptomatic patients.[1,2,7-10] Cross-sectional imaging studies on non-MoM bearings are, however, rare. Thus there remains some uncertainty about the clinical relevance of these findings.

In 2011, Williams et al[2] reported on pseudotumour formation in asymptomatic patients with either a RHA (n = 20), MoM THA (n = 31) or metal-on-polyethylene (MoP) THA (n = 24) screened by ultrasound. In their study, 4% of the patients with a MoP THA had a cystic mass and 8% had an isolated fluid collection. This incidence was lower than that for MoM RHA (30%) and large head MoM THA (42%).

Mistry et al[7] reporting on ten patients with an asymptomatic MoP and 12 patients with a MoM bearing, who were screened with MARS-MRI at a mean follow-up of 46 and 70 months, respectively, found eight periprosthetic fluid collections, of which one occurred in the MoP group.

Periprosthetic lesions, quantified as pseudotumour or MoM disease using currently available MARS-MRI scoring systems were encountered in our study. The incidence and grades of these lesions were similar in RHA and the CoP THA, at 17% and 18% respectively.

The lesions seen in our study were graded as 'pseudotumour' or 'MoM disease' when they met the criteria of at least one of the three classification systems. Every lesion was scored as an Anderson grade 'C'[12] varying from mild to severe MoM disease. Additionally, every lesion could be classified by the score of Hart et al[1]. One lesion in the RHA group

and one in the CoP group was scored as a Boomsma grade II lesion.[13] These were the only two patients who were not graded as pseudotumour by all three scores. In an earlier study of Bisschop et al,[10] only Boomsma grade IV and V lesions were considered to be clinically relevant. Applying a similar restriction to our study population, an incidence of pseudotumour of 11% in the RHA group and 12% in the CoP group would still have been encountered, once again resulting in similar incidences of pseudotumour. Obviously, the only solid lesions met were in the RHA group. However, perhaps only lesions scored as a Hart et al grade 3 are really clinically relevant.

Owing to the similar incidence of periprosthetic lesions in the RHA and CoP groups, the question of whether all periprosthetic lesions which are identified are 'real' pseudotumours arises. Some fluid collection is normal after any kind of THA without any destructive characteristics and without signs of infection in patients with good function and without pain. This is illustrated by the fact that in spite of the high grading on the different MRI classification systems, nine of 13 periprosthetic lesions were small (< 25 ml) fluid collections, in the presence of good clinical results and low metal ion levels. Therefore, we feel that there is a need for better MRI classification systems to reflect clinically relevant pseudotumours where a high grade actually corresponds with pathological and clinically relevant lesions. The presence of solid lesions, muscle damage and thickened capsule should be emphasised in seeking to define clinically relevant pseudotumours, as has been previously suggested.[20,21]

There remains no consensus on the most appropriate way of following up patients who have undergone a MoM arthroplasty and the indications for cross-sectional imagining remain unclear. Concerning the form of imaging, ultrasound, CT and MRI are used. Garbuz et al[22] showed that ultrasound and MARS-MRI performed equally well, with no significant difference in sensitivity or specificity between them. In addition to the uncertainty of which method of imaging should be adopted and the indications for cross-sectional imaging, the interpretation of the findings is also a matter of debate. Furthermore, the size of periprosthetic lesions changes over the course of time.[23,24] Serial MRI may have an important role in differentiating benign from pathological lesions.

We acknowledge the limitations of our study. Revisions were included in the two randomised MoM implant groups to maximise the follow-up for possible pseudotumour formation. In contrast, the matched control group of CoP THA patients originated from a series without complications which may have resulted in some bias towards a better clinical

outcome in this group. However, the absence of major differences in clinical outcome between the groups suggests that this did not have a great influence.

Secondly, patients in the control group were significantly ($p < 0.001$) older than those in the RCT (Table II). Initially patients were matched on three parameters: follow-up, gender and age. However, because of the relatively young age of the patients included in the RCT and a limited number of patients in our database, we had difficulty matching on all three parameters. Nevertheless, the mean age was only five years greater in the CoP group than in the RHA group. In our opinion the length of follow-up is the most important parameter, since pseudotumours tend to develop over time. Accordingly, matching by age was relegated to the last criterion.

Thirdly, grading the pseudotumours was performed by consensus without inter- or intra-observer reliability scoring. We accept the possibility that the junior radiologist might have deferred to the judgement of the senior radiologist. Nevertheless, we note that clinically relevant studies on this topic have almost exclusively been performed using a consensus.[1,10,25] In addition, Chang et al[26] found that there was only a moderate agreement (kappa 0.439) between two readers using the Anderson score.[12]

Fourthly, the number of periprosthetic lesions encountered in each group was relatively low for statistical testing. Owing to the low numbers, no conclusions can be drawn on clinical scores and grade of the lesions between the different prostheses groups.

Finally, no histological matching of aseptic lymphocyte-dominated vasculitis-associated lesion scores with the imaging findings was available in the patients who underwent a revision. The combination of MRI and histology would probably have given a better reflection of the true incidence but with only six revisions in our series, no true correlation between MRI findings and histology would have been possible.

We conclude that periprosthetic lesions can be identified in some arthroplasties of the hip with both MoM and CoP bearings when screened by MARS-MRI. A similar number of lesions in the RHA and CoP groups were graded as 'pseudotumour' or 'MoM disease' by three currently used systems of classification for pseudotumour. However, a substantial proportion of these lesions appear to reflect a benign collection of fluid or effusion without clinical significance. Despite the fact that pseudotumour formation after MoM arthroplasty of the hip remains a serious concern, currently available MRI scoring systems probably overestimate the incidence of clinically relevant pseudotumours post-operatively.

REFERENCES

1. Hart AJ, Satchithananda K, Liddle AD, et al. Pseudotumors in association with well-functioning metal-on-metal hip prostheses: a case-control study using threedimensional computed tomography and magnetic resonance imaging. *J Bone Joint Surg [Am]* 2012;94-A:317–325.
2. Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. Prevalence of pseudotumor in asymptomatic patients after metal-on-metal hip arthroplasty. *J Bone Joint Surg [Am]* 2011;93-A:2164–2171.
3. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res* 2012;470:1895–1906.
4. No authors lised. Metal-on-metal (MoM) hip replacements: medical device alert Ref: MDA/2012/016. Medicine and Healthcare Products Regulatory Agency. www.mhra.gov.uk (date last accessed 5 June 2015).
5. No authors listed. The use of metal-on-metal hip replacements: more strict advice to NOV members. Dutch Orthopaedic Association/Nederlandse Orthopaedische Vereniging (NOV). www.orthopeden.org (date last accessed 5 June 2015).
6. No authors listed. Concerns about Metal-on-Metal Hip Implant Systems. US Food and Drug Administration. www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/MetalonMetalHipImplants/ucm241604.htm (date last accessed 5 June 2015).
7. Mistry A, Cahir J, Donell ST, Nolan J, Toms AP. MRI of asymptomatic patients with metal-on-metal and polyethylene-on-metal total hip arthroplasties. *Clin Radiol* 2011;66:540–545.
8. Sabah SA, Mitchell AW, Henckel J, et al. Magnetic resonance imaging findings in painful metal-on-metal hips: a prospective study. *J Arthroplasty* 2011;26:71–76.
9. Toms AP, Marshall TJ, Cahir J, et al. MRI of early symptomatic metal-on-metal total hip arthroplasty: a retrospective review of radiological findings in 20 hips. *Clin Radiol* 2008;63:49–58.
10. Bisschop R, Boomsma MF, Van Raay JJ, et al. High prevalence of pseudotumors in patients with a Birmingham Hip Resurfacing prosthesis: a prospective cohort study of one hundred and twenty-nine patients. *J Bone Joint Surg [Am]* 2013;95-A:1554– 1560.

11. Fehring TK, Odum S, Sproul R, Weathersbee J. High frequency of adverse local tissue reactions in asymptomatic patients with metal-on-metal THA. *Clin Orthop Relat Res* 2014;472:517–522.
12. Anderson H, Toms AP, Cahir JG, et al. Grading the severity of soft tissue changes associated with metal-on-metal hip replacements: reliability of an MR grading system. *Skeletal Radiol* 2011;40:303–307.
13. No authors listed. Canadian Hip Resurfacing Study Group. A survey on the prevalence of pseudotumors with metal-on-metal hip resurfacing in Canadian academic centers. *J Bone Joint Surg [Am]* 2011;93-A (suppl 2):118–121.
14. De Smet KCP, Campbell P, Van der Straeten C. The Hip Resurfacing Handbook. Cambridge: Woodhead, 2013.
15. Van der Weegen W, Brakel K, Horn RJ, et al. Comparison of different pseudotumor grading systems in a single cohort of metal-on-metal hip arthroplasty patients. *Skeletal Radiol* 2014;43:149–155.
16. Bisseling P, Smolders JM, Hol A, van Susante JL. Metal ion levels and functional results following resurfacing hip arthroplasty versus conventional small-diameter metal-on-metal total hip arthroplasty; a 3 to 5year follow-up of a randomized controlled trial. *J Arthroplasty* 2015;30:61–67.
17. No authors listed. WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI. Ethical Principles for Medical Research Involving Human Subjects. Amended by the 59th WMA General Assembly, Seoul, October 2008. http://www.wma.net/en/ 30publications/10policies/b3/17c.pdf (date last accessed 14 July 2015).
18. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. *J Bone Joint Surg [Am]* 1969;51-A:737–755.
19. Amstutz HC, Thomas B J, Jinnah R, et al. Treatment of primary osteoarthritis of the hip: a comparison of total joint and surface replacement arthroplasty. *J Bone Joint Surg [Am]* 1984;66:228–241.
20. Nawabi DH, Gold S, Lyman S, et al. MRI predicts ALVAL and tissue damage in metal-on-metal hip arthroplasty. *Clin Orthop Relat Res* 2014;472:471–481.

21. Nawabi DH, Hayter CL, Su EP, et al. Magnetic resonance imaging findings in symptomatic versus asymptomatic subjects following metal-on-metal hip resurfacing arthroplasty. *J Bone Joint Surg [Am]* 2013;95-A:895–902.
22. Garbuz DS, Hargreaves BA, Duncan CP, et al. The John Charnley Award: diagnostic accuracy of MRI versus ultrasound for detecting pseudotumors in asymptomatic metal-on-metal THA. *Clin Orthop Relat Res* 2014;472:417–423.
23. Almousa SA, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. The natural history of inflammatory pseudotumors in asymptomatic patients after metal-on-metal hip arthroplasty. *Clin Orthop Relat Res* 2013;471:3814–3821.
24. Hasegawa M, Miyamoto N, Miyazaki S, Wakabayashi H, Sudo A. Longitudinal magnetic resonance imaging of pseudotumors following metal-on-metal total hip arthroplasty. *J Arthroplasty* 2014;29:2236–2238.
25. Hauptfleisch J, Pandit H, Grammatopoulos G, et al. A MRI classification of periprosthetic soft tissue masses (pseudotumours) associated with metal-on-metal resurfacing hip arthroplasty. *Skeletal Radiol* 2012;41:149–155.
26. Chang EY, McAnally JL, Van Horne JR, et al. Metal-on-metal total hip arthroplasty: do symptoms correlate with MR imaging findings? *Radiology* 2012;265:848– 857.

Principles for Medical Research
General Assembly, Seoul, October 2008.
b3/17c.pdf (date last accessed 14 July 2015).

18. Harris WH. Traumatic arthritis of the hip after dislo
by mold arthroplasty. An end-result study using a new m
Surg [Am] 1969;51-A:737–755.

19. tz HC, Thomas B J, Jinnah R, et al. Treatment of p
comp of total joint and surface replacement arthr
1984;66:22

20. Nawabi DH, Gol man S, et al. MRI predicts ALVAL and
hip arthroplasty. *Clin O Relat Res* 2014;472:471–481.

CHAPTER 7

The absence of a metal-on-metal bearing does not preclude the formation of a destructive pseudotumour in the hip - a case report

Pepijn Bisseling, Timothy Tan, Zhen Lu,
Pat A Campbell, Job L C Susante

Acta Orthop. 2013; 84 (4): 437–441.

CASE

In 2009, a 62-year-old woman with rheumatoid arthritis and a total hip arthroplasty (THA) on the right (uncemented Ti-6AL7Nb stem combined with a Ti threaded cup, polyethylene inlay, and a 28-mm ceramic head; Zweymuller Alloclassic; Zimmer Orthopaedics, Warsaw, IN) implanted in 2006 presented with a left femoral neck fracture. A THA with a double-mobility acetabular system (Avantage Double-Mobility Acetabular System; Biomet, Warsaw, IN) was implanted. An uncemented titanium-niobium (Ti-6Al-7Nb) stem was used (Zweymuller Alloclassic; Zimmer) with a 12/14 mm trunnion combined with an XXL (+10.5 mm) 28-mm cobalt-chromium head with a 12/14 mm tapered bore (Biomet). The femoral head was introduced into the highly cross-linked, vitamin E-stabilized polyethylene bearing using a bearing press. An uncemented Ti HA-coated 52-mm acetabular shell was press-fitted in the socket and the large polyethylene femoral head was reduced into the metal articular surface. Postoperative recovery was uneventful, with normal wound healing.

Two years after implantation, the patient was referred to our center by her rheumatologist, since a soft tissue mass adjacent to the left THA had been diagnosed by ultrasound. A standard AP pelvic radiograph revealed adequate positioning of both hip implants without any signs of wear or osteolysis. Subsequent MARS-MRI scanning confirmed the presence of a 6 × 9 cm soft tissue mass at the posterolateral aspect of the left greater trochanter (Figure 1). There were no signs of any soft tissue reaction around the contralateral THA.

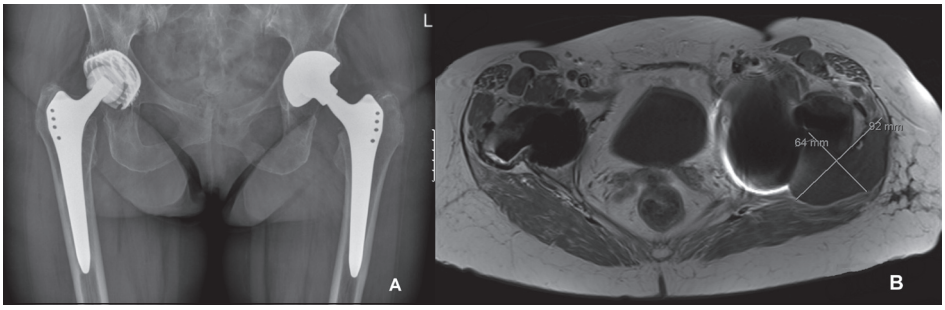


Figure 1. Standard AP radiograph (panel A) and MARS-MRI scan (panel B) 2 years after implantation of the left THA with a double-mobility acetabular component.

Note the adequate implant positioning and fixation (A) and a 6 × 9 cm soft tissue mass (B) at the posterolateral side of the left femoral component. On the right, there were no signs of periprosthetic soft tissue reaction.

CRP was 68 mg/L and ESR was 53 mm/h; both were elevated, but this was possibly related to her rheumatoid arthritis. An inductively-coupled plasma mass spectrometer (ICP-MS) was used for evaluation of metal ion levels. Serum levels of chromium were below the detection level of 0.5µg/L, whereas cobalt serum levels were 5.7 µg/L. An aspirate of the hip joint was negative for bacterial or fungal growth.

The patient was diagnosed as having a severe and early "adverse local tissue reaction" (ALTR) after a metal-on-polyethylene bearing THA with the taper as the potential source of the metal ion release. Two and a half years after implantation, a debulking procedure of the pseudotumour in combination with a one-stage revision of the femoral component was performed.

Perioperatively, extensive tissue necrosis and partial destruction of the abductor mechanism were found in the absence of any macroscopic signs of infection. The acetabular component was well fixed. Both the femoral trunnion and bore of the head showed signs of black debris (Figure 2). The femoral component was revised to a cemented polished straight stem (Exeter; Stryker, Allendale, NJ) with a ceramic 28-mm head (also Stryker) and a new double-mobility liner (Avantage Double-Mobility Acetabular System; Biomet). At the revision operation, six tissue samples were taken for bacterial culture according to our protocol. All six samples were negative for bacterial growth.

The revision procedure was complicated by a deep infection that was unresponsive to lavage and prolonged antibiotic treatment. Two months after revision, all components had to be removed, resulting in a (temporary) Girdlestone situation.

The components were sent for retrieval analysis. Multiple samples of the periprosthetic tissues were processed in paraffin for routine histology. The histopathology of tissue samples revealed extensively necrotic material with only a focal cellular area of inflammatory cells containing macrophages, plasma cells, occasional foci of eosinophils, and several small perivascular lymphocytic aggregates (Figure 3). No polarizable materials or metallic debris were present in several tissue samples. The ALVAL score[1] was 3 + 3 + (= 8/10, moderate). Overall, the histological profile was consistent with an adverse immunological reaction in the absence of visible wear debris.

The profile of the ball taper was measured using a coordinate measuring machine (Legex 322; Mitotoyo, Aurora, IL). The dimensions of a perfect taper based on 6726 CMM points with a point spacing of 0.3 mm were determined using a least-squares method. The taper

had an angle of 5 degrees, 47 min, and 34 s. A contour map was generated using the deviations of the CMM points from the fitting taper (Figure 4). The CMM results indicated uneven areas of contact, but the amount of material that had been removed through wear or corrosion could not be determined without knowing the initial form of the parts. However, in combination with the microanalysis described below, it appears that the small degree of texture and color changes was consistent with mild corrosion.

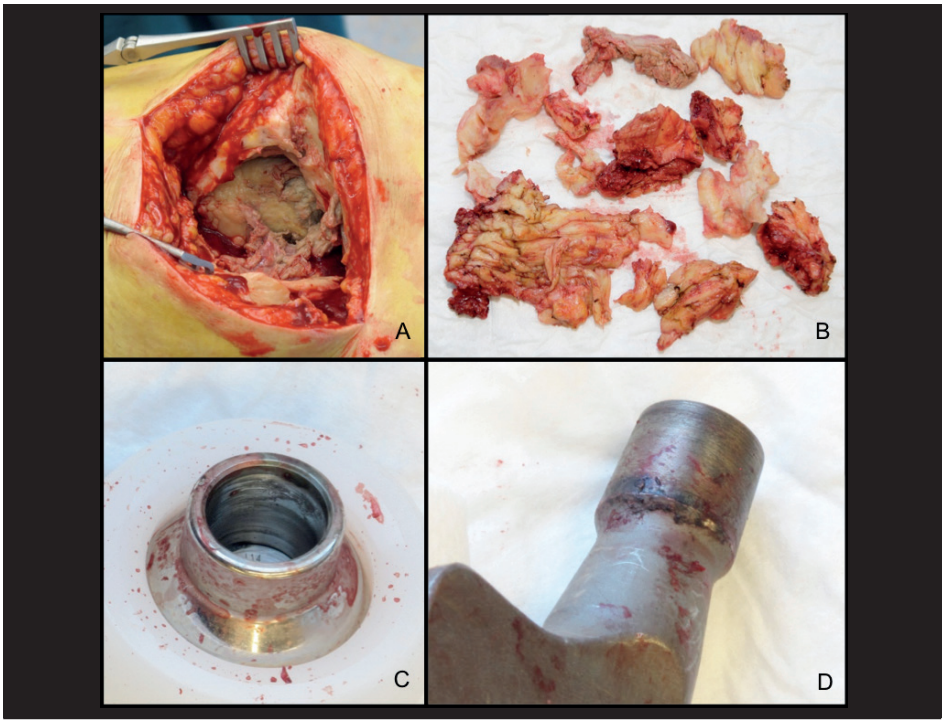


Figure 2.
A) Extensive necrosis at the greater trochanter area and destruction of the abductor mechanism.
B) Debulking of large amounts of necrotic and fibrotic tissue from the periprosthetic region.
C and D) Macroscopic signs of corrosion products at the bore of the Co-Cr head (panel C) and at the trunnion of the femoral component (panel D).

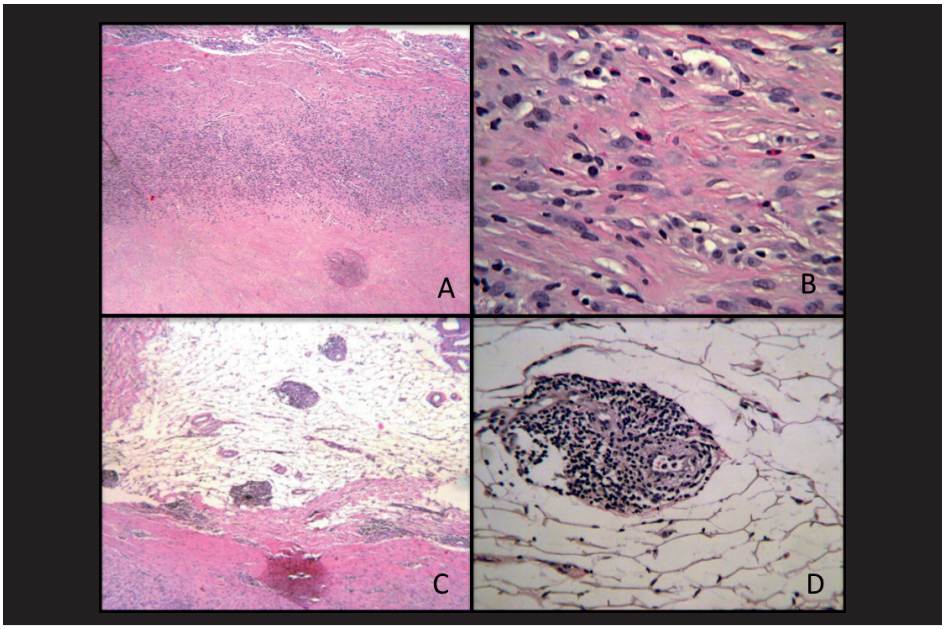


Figure 3.
A) Histological view of the soft tissue mass at the interface between the necrotic material (on the joint side) and inflammatory cells. Hematoxylin and eosin (HE), 40×. **B)** Enlargement of A with inflammatory cells consisting mainly of macrophages and lymphocytes along with plasma cells and eosinophils. HE, 200×. Several lymphocytic aggregates were observed at low magnification (panel C; HE, 40×) and at high magnification (panel D; HE, 200×).

The area of the stem trunnion that appeared discolored was examined by scanning electron microscopy (SEM) and energy-dispersive analysis of X-rays (EDAX) to identify the elements present. Organic material containing chromium and/or molybdenum consistent with corrosion products was identified within the machined grooves and in the deposited dark material outside the trunnion (Figure 5). Similar analysis performed on deparaffinized soft tissue sections failed to demonstrate any wear or corrosion products.

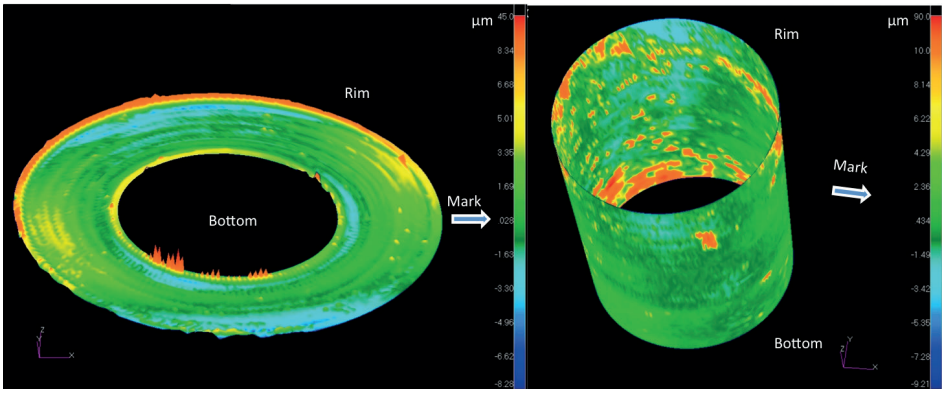


Figure 4.
A) 2-dimensional graphical representation of the same profile. The outer diameter of the CMM map is the portion of the taper closest to the stem (labeled Rim) and the inner diameter of the CMM image corresponds to the inner surface (labeled Bottom). Areas with differences in color intensity may be related to wear or corrosion from the original dimensions.
B) 3-dimensional map with the portion closest to the stem labeled Rim and the deepest portion of the taper closest to the bearing surface labeled Bottom. Note the uneven distribution of color, corresponding to differences in contact with the trunnion.

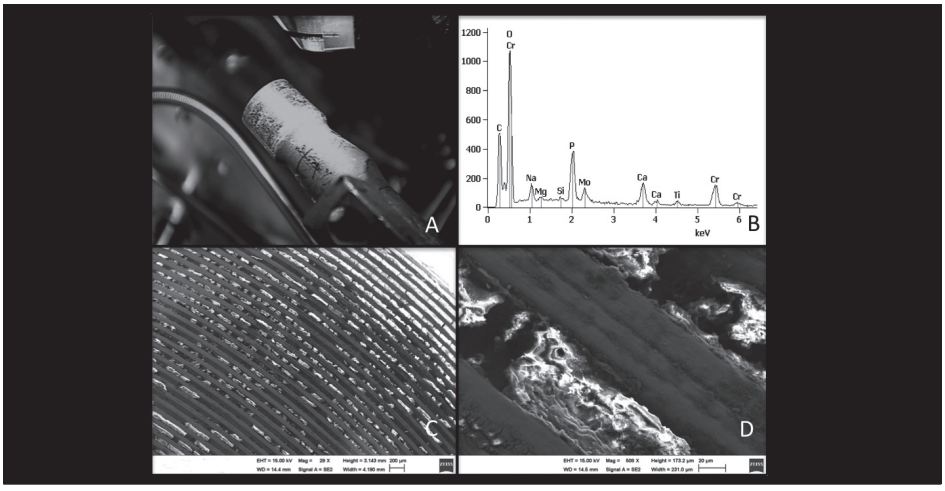


Figure 5. Material present on the trunnion of the femoral component (panel A) was investigated by EDAX, revealing chromium (Cr), molybdenum (Mo), and oxygen (O) peaks consistent with corrosion products (panel B). The organic material within the grooves containing chromium oxides is shown at approx. 30× (panel C) and 500× magnification (panel D).

DISCUSSION

We describe a patient with a rapidly forming, large and destructive pseudotumour as a form of ALTR after a THA with a double-mobility metal-on-polyethylene bearing. The exact pathogenesis of periprosthetic adverse reactions is still unknown, but a frequently suggested hypothesis is the contribution of wear particles and ions from corrosion, particularly from articulating surfaces of MoM hip implants.[1-4] However, any MoM connection in a total hip arthroplasty could theoretically be a source of metal debris and ions. These MoM connections are diverse, with increasing modular options. The exact origin of the metal debris is often obscure, with the combined use of modular MoM junctions and MoM articulating bearings in the same implant.[5,6] Numerous authors have reported higher metal ion levels and incidences of ALTR after largediameter MoM total hip arthroplasty (THA) than after resurfacing hip arthroplasty (RHA) using identical articulation characteristics.[6,7] The latter lacks any modular MoM junctions, which may explain the difference encountered. To date, there is very little literature available to explain the extent to which the taper contributes to the release of metal particles, corrosion products including ions, and ALTR.[4,5,8-11]

Our case is interesting, as the ALTR could only have been triggered by metal ion release from the head-neck taper junction since no other MoM articulating surface was used. ALTR can also be associated with polyethylene wear.[12] However, in this case polyethylene wear was not a likely cause of the massive pseudotumour since the hip arthroplasty was only 2 years in situ, which is a short time for abundant polyethylene wear to occur, and this is consistent with the lack of polyethylene debris in the tissues.

Furthermore, the SEM and EDAX analysis showed corrosion products on the trunnion. Corrosion and wear at this modular head-neck junction can occur when a passive protective oxide film on the metallic surfaces is constantly disrupted by fretting and micromotion.[13,14] The extent of the corrosion process is affected by a number of factors, including the amount and quality of metallic junctions and forces that are projected on the junctions.[14-17] In our case, several factors may have contributed to the release of metal corrosion products from the head-neck junction together with the rapid formation of a massive pseudotumour. First, the quality of the tapered head-neck junction may have been impaired by a subtle mismatch between components from different manufacturers. Both the head and neck had a 12/14 taper, which indicates a gradual decrease in diameter from 14 mm to 12 mm. In contrast

to what is commonly believed, a 12/14 taper is not standard and can reveal subtle inter- and intra-manufacturer differences between components. In fact, it is the angle by which the taper goes from 14 to 12 mm that truly determines its profile. This angle is expressed in degrees, minutes, and seconds where 1 degree is made up of 60 minutes and 1 minute has 60 seconds. In our case, according to manufacturer-derived data, the implanted stem trunnion had a 12/14 taper with a 5-degree, 38-min, and 0-s taper, and the head had a 5-degree, 42-min, and 30-s taper. The amount of manufacturing tolerance of these parts is not known but the ball taper was demonstrated by CMM to be 5 degrees, 47 min, and 34 s, which may reflect the allowable tolerance, the effect of wear or corrosion, or a combination of the two. Even a subtle angular mismatch between the trunnion and taper may have led to an incongruence of the head-neck junction, leading to increased wear and corrosion. The release of metal debris from a modular junction due to a mismatch of components from different manufacturers has recently been addressed by Chana et al.[18] However, reports on release of metal debris from the head-neck junction are also available with the use of components from the same manufacturer.[9] This may be related to the fact that for a given taper from one manufacturer, the angle may also differ by a few minutes of a degree within the accepted range of tolerance. This tolerance is generally higher for ceramic heads than for metallic ones as used in this case.[19]

Secondly, the corrosion may partly be explained by increased mechanical stresses on the head-neck junction. In a sense, the double-mobility acetabular system mimics the configuration of a large-diameter femoral head. An increase in head diameter may cause the frictional force between the articulating surfaces to produce a greater frictional torque at the head-neck interface and may facilitate mechanically assisted fretting corrosion. Similarly, when the articulating surface is medialized with a large-diameter head, the frictional torque may be increased on the taper junction due to the greater length of arm. Forces on the taper may be even further increased when longer necks are used. Brown et al. found a correlation between corrosion and the length of neck extensions.[15] They concluded that longer head-neck extensions may be more susceptible to fretting and crevice corrosion because of instability at the interface. This was also confirmed in a study by Lavigne et al., where higher cobalt ion levels were seen in patients with longer sleeve lengths than in those with shorter lengths at 12 months of follow-up.[20] In our case, the double-mobility system may have led to greater stresses on the taper junction according to the same principle that

applies to large-diameter head THAs. A +10.5-mm (XXL) extended head increased the lever arm and applied even greater forces to the taper junction. Although contact stress may account for the contour irregularities observed (Figure 4), corrosion may have occurred without the presence of contact stress, which makes it difficult to definitively attribute the contour irregularities to contact stress alone.

Apart from the relatively increased lever arm and the possible taper mismatch, important patient factors may also have had a role in the formation of this destructive pseudotumour. Unknown patient susceptibility factors or metal hypersensitivity could explain pseudotumour formation.[1,21-23] In a study by Matthies et al., pseudotumours were common in patients with well-positioned prostheses and were not necessarily associated with high wear or high metal ion levels.[22] Moreover, Hart et al. found that a considerable proportion of unexplained hip pain could not be related to either excessive wear or elevated metal ion levels.[21] They proposed that a patient susceptibility factor caused at least a proportion of the hip arthroplasty failures. Our patient may have been more vulnerable to developing ALTR due to her history of rheumatoid arthritis. In addition, corrosion at the trunnion from her earlier contralateral THA may have alerted her immune system to the metal debris released at the pseudotumour side. The rapid formation of the mass, the impressive surgical and histological findings in the surprising absence of substantial wear, and only moderate levels of ions may be explained by heightened sensitivity. The histological evaluation was based on only a small area of viable tissue but the features were comparable to several other cases with low wear-related pseudotumours attributed to metal allergy.[1] Although rheumatoid arthritis and metal hypersensitivity share lymphocytic predominance as a characteristic immunohistological feature, no studies have supported the association between rheumatoid arthritis and ALTR. However, given the profound immune response in rheumatoid arthritis, it is conceivable that rheumatoid arthritis may enhance the development of ALTR.

Finally, an Alloclassic uncemented titanium-niobium (Ti6A/7Nb) stem was combined with a cobalt-chromium (Co-Cr) articulating prosthetic head. Differences in electrical potential may cause galvanic corrosion when two different metals are in contact in an electrolyte solution.[14] There is evidence that mixed-alloy combinations are associated with a higher corrosion incidence than similaralloy combinations.[8,16,17] However, the role of galvanic corrosion in the latter is still debated, whereas the electrochemical gradient between Co-Cr and Ti alloys is said to be small.[24] In our patient, the fact that there were

relatively low chromium ion levels (0.5 µg/L) relative to cobalt levels in serum (5.7 µg/L) makes it likely that there was corrosion.

In conclusion, we believe that several factors have had a role in the development of a severe ALTR in our patient. It is most likely that we were confronted with a profound patient-related immunological response to a moderate amount of metal debris and corrosion products from the mismatched head-neck junction. One should be aware that, with or without a MoM articular bearing, the head-neck junction may also be a source of metal debris and corrosion products and can then trigger the development of ALTR. In spite of the fact that there are also subtle taper mismatches between components from the same company, mixing components from different companies should be avoided if possible.

REFERENCES

1. Campbell P, Ebramzadeh E, Nelson S, Takamura K, De Smet K, Amstutz HC. Histological features of pseudotumor-like tissues from metal-on-metal hips. *Clin Orthop Relat Res* 2010;468-9:2321-7.
2. Kwon YM, Glyn-Jones S, Simpson DJ, Kamali A, McLardy-Smith P, Gill HS, Murray DW. Analysis of wear of retrieved metal-on-metal hip resurfacing implants revised due to pseudotumours. *J Bone Joint Surg Br* 2010;92-3:356-61.
3. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *J Bone Joint Surg Br* 2010;92-1:38-46.
4. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, Ostlere S, Athanasou N, Gill HS, Murray DW. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* 2008;90-7:847-51.
5. Langton DJ, Jameson SS, Joyce TJ, Gandhi JN, Sidaginamale R, Mereddy P, Lord J, Nargol AV. Accelerating failure rate of the ASR total hip replacement. *J Bone Joint Surg Br* 2011;93-8:1011-6.
6. Vendittoli PA, Amzica T, Roy AG, Lusignan D, Girard J, Lavigne M. Metal Ion release with large-diameter metal-on-metal hip arthroplasty. *J Arthroplasty* 2011;26-2:282-8.
7. Garbuz DS, Tanzer M, Greidanus NV, Masri BA, Duncan CP. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: a randomized clinical trial. *Clin Orthop Relat Res* 2010;468-2:318-25.
8. Collier JP, Surprenant VA, Jensen RE, Mayor MB, Surprenant HP. Corrosion between the components of modular femoral hip prostheses. *J Bone Joint Surg Br* 1992;74-4:511-7.
9. Cooper HJ, Della Valle CJ, Berger RA, Tetreault M, Paprosky WG, Sporer SM, Jacobs JJ. Corrosion at the head-neck taper as a cause for adverse local tissue reactions after total hip arthroplasty. *J Bone Joint Surg Am* 2012;94-18:1655-61.
10. Gill IP, Webb J, Sloan K, Beaver RJ. Corrosion at the neck-stem junction as a cause of metal ion release and pseudotumour formation. *J Bone Joint Surg Br* 2012;94-7:895-900.
11. Vundelinckx BJ, Verhelst LA, De Schepper J. Taper Corrosion in Modular Hip Prostheses: Analysis of Serum Metal Ions in 19 Patients. *J Arthroplasty* 2013.

12. Leigh W, O'Grady P, Lawson EM, Hung NA, Theis JC, Matheson J. Pelvic pseudotumor: an unusual presentation of an extra-articular granuloma in a well-fixed total hip arthroplasty. *J Arthroplasty* 2008;23-6:934-8.
13. Gilbert JL, Buckley CA, Jacobs JJ. In vivo corrosion of modular hip prosthesis components in mixed and similar metal combinations. The effect of crevice, stress, motion, and alloy coupling. *J Biomed Mater Res* 1993;27-12:1533-44.
14. Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am* 1998;80-2:268-82.
15. Brown SA, Flemming CA, Kawalec JS, Placko HE, Vassaux C, Merritt K, Payer JH, Kraay MJ. Fretting corrosion accelerates crevice corrosion of modular hip tapers. *J Appl Biomater* 1995;6-1:19-26.
16. Goldberg JR, Gilbert JL. In vitro corrosion testing of modular hip tapers. *J Biomed Mater Res B Appl Biomater* 2003;64-2:78-93.
17. Goldberg JR, Gilbert JL, Jacobs JJ, Bauer TW, Paprosky W, Leurgans S. A multicenter retrieval study of the taper interfaces of modular hip prostheses. *Clin Orthop Relat Res* 2002-401:149-61.
18. Chana R, Esposito C, Campbell PA, Walter WK, Walter WL. Mixing and matching causing taper wear: corrosion associated with pseudotumour formation. *J Bone Joint Surg Br* 2012;94-2:281-6.
19. Hallab NJ, Mikecz K, Vermes C, Skipor A, Jacobs JJ. Differential lymphocyte reactivity to serum-derived metal-protein complexes produced from cobalt-based and titanium-based implant alloy degradation. *J Biomed Mater Res* 2001;56-3:427-36.
20. Lavigne M, Belzile EL, Roy A, Morin F, Amzica T, Vendittoli PA. Comparison of whole-blood metal ion levels in four types of metal-on-metal large-diameter femoral head total hip arthroplasty: the potential influence of the adapter sleeve. *J Bone Joint Surg Am* 2011;93 Suppl 2:128-36.
21. Hart AJ, Matthies A, Henckel J, Ilo K, Skinner J, Noble PC. Understanding why metal-on-metal hip arthroplasties fail: a comparison between patients with well-functioning and revised birmingham hip resurfacing arthroplasties. AAOS exhibit selection. *J Bone Joint Surg Am* 2012;94-4:e22.
22. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res* 2012;470-7:1895-906.

23. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005;87-1:28-36.
24. Lucas LC, Buchanan RA, Lemons JE. Investigations on the galvanic corrosion of multialloy total hip prostheses. *J Biomed Mater Res* 1981;15-5:731-47.

Hallab NJ, Mikecz K, Vermes C,
serum-derived metal-protein complexes
implant alloy degradation. *J Biomed Mater Res*
20. Lavigne M, Belzile EL, Roy A, Morin F, Amzica
blood metal ion levels in four types of metal-on-metal
arthroplasty: the potential influence of the adapter sleeve.
36.
21. Hart
tthies A, Henckel J, Ilo K, Skinner J, Noble P
metal hip a
lasties fail: a comparison between patients w
birmingham hip
cing arthroplasties. AAOS exhibit s
2012;94-4:e22.
Matthies AK, Skinner JA, Os
Henckel J, Hart AJ. Pse
positioned low-wearing metal-on-m
ips. *Clin Orthop*

CHAPTER 8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

The objective of this thesis was to focus on the clinical results of a prospective randomised clinical trial that compared a metal-on-metal (MoM) resurfacing hip arthroplasty (RHA) to a MoM small-diameter head conventional type of total hip arthroplasty (MOM THA). In addition, it aimed to enhance understanding on the potential adverse reactions related to MoM bearings, together with the evaluation and interpretation of both metal ion analysis and cross-sectional imaging. Seven objectives were formulated. The objectives are discussed in this summary, which is divided into two sections that discuss the 'clinical results' and the difficulties that are encountered when screening for 'Adverse Reactions to Metal Debris' (ARMD)' respectively.

Clinical results

1. Determination of the effect of preference bias for a specific implant on satisfaction and short-term clinical outcomes.

In the early years of the 2000s, the global demand for RHA rose, which led to the accelerated introduction of several brands of RHA on the market and a rise in their use.[1] However, long-term clinical results on many of the implants were lacking. The potential disadvantages, such as a more technically demanding procedure, the occurrence of excessive metal ion release and ARMD were less widely specified.[2-4] In order to evaluate the clinical results of the RHA, a randomised clinical trial was set up, in which the RHA was compared to a MoM THA.

A randomised trial is the ideal instrument for an objective comparison between two different implant types. As in this thesis, a new implant, such as a resurfacing implant, is compared to a 'golden standard' - a conventional type of MoM THA. By randomisation, the effects of potential confounding factors are minimalised, such as preference bias. Nevertheless, at time of the study start-up, it proved to be extremely difficult to include patients due to the randomisation between RHA and MoM THA. At that time, the RHA was marketed as a 'sports' hip, and an ideal solution for young and active patients. Young patients, who visited the orthopaedic outpatient clinic and were candidates for a total hip arthroplasty

were invited to participate in the randomised clinical trial. Even after being informed of the absence of any evidence in literature about the benefits of RHA over a conventional THA, patients tended to have a profound preference for RHA and often declined participation in the randomised trial. Patients with a profound preference for RHA, who declined inclusion in the study, were invited to participate in a cohort of patients with an identical follow-up to the randomised clinical trial. It is questionable if the patients included in the cohort were biased for subjective clinical scores due to their profound preference. The presence of a cohort of patients with a clear preference for RHA and a group of patients allocated to RHA after randomisation with an identical study set-up, provided the opportunity to gain some insight into the possible role of 'preference biases' on the outcome of the same surgical procedure.

Chapter 2 presents the results of the prospective comparative study. Results on patient satisfaction and early clinical outcome in 'biased' patients with a high preference for RHA (the 'Preference' Group) did not differ with any statistically significance from the results obtained from 'unbiased' patients, who were simply allocated to a RHA after randomisation ('Randomised' Group). Nevertheless, there was a trend toward a better satisfaction in the 'Preference' Group. A statistically significant difference between groups was only encountered specifically for the preoperative Short Form-12 values, for the mental subscale in particular, with this in favour of the 'Randomised' Group.

Despite the fact that the potential bias from treatment preferences is a well-recognised phenomenon in orthopaedic practice, there have only been a few studies dealing with this clinical dilemma. The results of this study contradict with a meta-analysis, in which preference for a specific treatment among patients in musculoskeletal trials was associated with treatment effects.[5] The difference between this study and the meta-analysis might be caused by a slightly different situation, in which the decision to operate is already satisfactory for many patients. This may differ for trials that compare operative- with conservative therapies, in which compliance with a therapy is another factor. This is supported by the fact that in this study, both 'Preference' and 'Randomised' Groups showed high satisfaction scores.

2. Obtaining an objective comparison between the clinical results of a metal-on-metal resurfacing hip arthroplasty and a small-diameter head metal-on-metal total hip arthroplasty at mid-term follow-up.

The clinical results of the randomised clinical trial that compared RHA and a MoM small-diameter head THA (MoM THA) after a three- to five-year follow-up are given in **Chapter 3**. From June 2007 until January 2010, 71 patients under the age of 65 years were randomly assigned to receive either a Conserve® Plus RHA (Wright Medical Technology, Arlington, Tennessee, USA) (n=38) or a 28-mm metal head Zweymuller® Classic Metasul® THA (Zimmer Orthopaedics, Warsaw, Indiana, USA) (n=33). All patients reached the 36 month follow-up point, and approximately 50% of the patient participated in a five-year follow-up. As expected, the functional results showed a highly significant improvement in the postoperative five years for both RHA and MoM THA. The Visual Analogue Scale (VAS) for satisfaction, Oxford Hip Score (OHS) and University of California Los Angeles activity score (UCLA), revealed a significant difference in favour of the RHA Group at some short term time intervals, but this difference resolved at further follow-up. In general, it seems that the RHA patients performed slightly better than the MoM THA patients in the first two years after surgery, but after three years, no major clinical significant differences in functional outcome could be demonstrated. These findings correspond with earlier studies that also found some significant differences in favour of the RHA at short term, but no significant differences at mid- or long-term follow-up.[6,7]

Concerning the survival of both implants, at five year follow-up, six patients were re-operated; three in the RHA group (8%) and three in the MoM THA group (9%). At two year follow-up, two MoM THA patients underwent a relatively simple insert exchange for recurrent dislocation, and one RHA patient had a femoral component revision, because of early aseptic loosening from avascular necrosis. The other three re-operations were related to adverse reactions to metal debris (ARMD).

Until a two year follow-up, no revisions for ARMD, or pseudotumours, as they are generally referred to, had occurred. Various serious adverse reactions to MoM bearings have been reported in literature in the years after reintroduction. These have included implant-

induced hypersensitivity reactions, osteolysis, soft tissue necrosis and solid or fluid-filled pseudotumours.[8-11]. The reported prevalence of the pseudotumours range from 0.1% to 67% and seems to increase latterly.[12-14] Due to these reports, a peak of revisions due to pseudotumour formation was feared in the randomised clinical trial in the period after two-year follow-up. However, this turned out to not to be the case (Chapter 3). At three-year follow-up, three patients, one MoM THA and two RHA patients had a symptomatic pseudotumour that mandated revision to an alternative bearing. Interestingly, one of these pseudotumours was encountered in the conventional MoM THA group. The occurrence of pseudotumours in this group is rather remarkable, since pseudotumours in patients with a 28-mm MoM THA are not commonly described in literature. Two studies reported a 0.5–1.8% revision rate, because of ARMD after a 28-mm diameter head MoM THA in a period of up to ten-year follow-up.[15,16] In this study, one pseudotumour out of 33 patients implicated a prevalence of 3% in a period of up to five-year follow-up, which is rather high, when compared to the numbers given in literature.

In contrast, the prevalence of pseudotumours in patients with a RHA (5%) encountered in the randomised clinical trial is relatively low compared to the prevalence given in literature that rose up to 67%.[12,14] However, it has to be noted that cross-sectional imaging was not a part of in this study. This may explain the relative low number of encountered pseudotumours. Cross-sectional imaging was performed in a subsequent study, and is presented in Chapter 6.

The true incidence, pathogenesis and clinical significance of adverse reactions registered as ARMD remains indistinct. This is influenced by the fact that the pathogenesis is affected by a variety of factors, such as wear, implant design, size, positioning and patient specific characteristics that differ between reports. Moreover, there is still no clear definition of clinical relevant pseudotumours or ARMD. As a result, the prevalence of pseudotumours given in literature is rather widespread.

Screening methods for Adverse reactions to metal debris

Due to the occurrence of ARMD, several guidelines were developed to for the screening of patients with a MoM bearing. These guidelines generally recommend: clinical evaluation; metal ion analysis; and cross-sectional imaging. The analysis of metal ions was included

in the guidelines driven by studies that related the evolution of ARMD to elevated metal ion levels in patients with a MoM implant.[8,9,17] Moreover, it is proposed that cobalt and chromium levels correlate with linear and volumetric wear, and can function as an indicator of bearing performance and wear.[18,19] The metal ions can be detected in various matrices, such as whole blood, serum and urine after implantation of a metal-on-metal bearing implant. Since urine sampling requires a 24-hour collection, and levels seem to be more variable due to variation in hydration of the patient, whole blood and serum are preferred. Patients enrolled in the randomised clinical trial were evaluated for metal ion concentrations in whole blood and serum at regular intervals.

3. Determination of the difference in metal ion release between a large-diameter head resurfacing arthroplasty and a small-diameter head total hip arthroplasty.

A prospective follow-up of cobalt- and chromium ion levels in whole blood and serum in a group of patients with an RHA versus a small-diameter head MoM THA is presented in **Chapter 3**. Both the RHA- and the MoM THA Groups revealed a chronological curve of cobalt and chromium blood levels, representing an increase during a running-in phase of one year and stabilising (cobalt) or decreasing (chromium) afterwards. Regardless, the implant group median metal ion levels remained well-below the safety cut-off level of 2.0 µg/l for cobalt and chromium given by the Dutch Orthopaedic Association (NOV), and far below the limits given by the United Kingdom's (UK's) Medicines and Healthcare products Regulatory Agency (MHRA) (cobalt 119 nmol/l = 7.0 µg/l; chromium 134.5 nmol/l = 7.0 µg/l).[20,21] Within the safety zone of below 2.0 µg/l, overall cobalt and chromium levels were significantly higher for the RHA group. This difference tended to fade at five-year follow-up, when RHA levels tended to decline. For chromium especially, a gradual decrease with longer follow-up in both groups was observed. Unlike some reports on a variety of RHA devices, the metal ion levels in both the RHA and MoM THA groups appeared to be rather low.[22,23] Implant-related factors and component positioning are believed to play an essential factor in the metal ion levels encountered.

4. Determining if metal ion concentrations in whole blood and serum can be used interchangeably, and if a formula can give a reliable conversion from serum to whole blood.

Metal ion level measurements were proposed as an indicator for wear and implant malfunctioning, and it was expected that orthopaedic surgeons would be able to interpret them. The interpretation was, however, obscured by an absence of a consensus in literature on the superiority of measurements in whole blood over serum or vice versa. Furthermore, cut off points are not always specified as levels in serum or whole blood. Since metal ion levels between both matrices differ, it is important to know if whole blood and serum can be used interchangeably.

In **Chapter 4,** an analysis into if metal ion concentrations in whole blood and serum could be used interchangeably was performed and if a formula could give a reliable conversion from serum to whole blood. Patients from the randomised clinical trial were combined with patients of the cohort with a high preference for RHA (Chapter 2), resulting in a group of 60 RHA and 32 MoM THA patients. A total of 343 serum- and whole blood samples were available for analysis. The mean cobalt serum levels were slightly lower or equivalent to whole blood represented by a mean difference of +0.13 µg/l (95%-CI:0.03;0.22). The opposite holds for chromium, in which serum levels were relatively higher compared to whole blood, indicated by a mean difference of -0.91 µg/l (95%-CI:-1.05;-0.77). Based on these differences and the wide limits-of-agreement of the Bland-Altman plot (Cobalt +1.5 µg/l and -1.25 µg/l; Chromium +0.95 µg/L and -2.85 µg/l), it appears that the two blood fractions cannot be used interchangeably.

Formulae to convert whole blood values into serum values were generated from the available data (Chapter 4).

*Cobalt in whole blood = 0.34 + (0.88*cobalt in serum)*
*Chromium in whole blood = 0.14 + (0.58*chromium in serum)*.

These formulas could not be validated from the study's own data and an additional database was not available. To reach limits of agreement, a new formula was generated on half of the data and tested on the other half. This new formula provided limits of agreement of +0.77 µg/l and -0.84 µg/l for cobalt and +0.92 and -0.98 µg/l for chromium. However, the formula was obtained from testing only on a homogeneous group of patients and requires verification on external data and a more heterogeneous group before it can be used in practice. Nonetheless, the conversion formula could offer reassurance to the clinician in interpretation of metal ion levels if only serum levels are available and vice versa, accepting a prediction error of less than 1.0 µg/l.

From the data used, whole blood cannot be recommended over serum or vice versa. From a practical perspective, the use of whole blood may be preferred, since whole blood can be sent to the laboratory without separation of serum. Obtaining an adequate and reliable measurement of ultra-low levels of metal ions is a delicate process and is susceptible to potential contamination. The separation of serum from whole blood can introduce contamination into the sample, which can result in an incorrect high metal ion test result. Alongside contamination and implant-related factors, metal ion levels may also be influenced by patient specific factors, such as renal excretion. Moreover, high levels can also be related to other sources of metal ion release, such as; mechanical heart valves, orthodontic implants, medical or nutritional supplements containing metal ion 'equivalents', or environmental or occupational sources of metal contamination. All of these confounding factors should be taken into consideration when confronted by high metal ion levels.

The potential toxic risk of high metal ion levels remains a point of debate. The carcinogenic potential, generalised hypersensitivity reactions, cardiomyopathy, neurological damage, hypothyroidism, renal impairment and a change in psychological status, have all been suggested to be associated with elevated metal ion levels, but others question the risks and state that solid epidemic studies are missing.[24-28]

Despite the lack of evidence on the potential toxic effect of high metal ion levels, it is important for clinical practice to know if measured metal ion levels are within acceptable levels. A uniform international consensus on acceptable metal ion levels is, nevertheless,

lacking. Several national- and international regulatory bodies and orthopaedic societies have defined their own metal ion reference values. The MHRA has established its own acceptable limits at 7.0 µg/l (for cobalt and chromium), and the NOV has defined the safety cut-off at 2.0 µgl (for cobalt and chromium) and warrants close follow-up for values between 2.0-5.0 µg/l.[20,21] These proposed limits are generally based upon available literature on metal ion levels and clinical results rather than on toxicity. As per the study of Van der Straeten et al. metal ion levels in patients with a well-functioning RHA were compared to malfunctioning RHA. In the well-functioning group, metal ions levels were lower than the poorly functioning group ion levels. Acceptable upper levels in serum were defined at 4.6 µg/l and 4.0 µg/l for chromium and cobalt respectively, for unilateral RHA. Metal levels higher than these proposed safe upper limits were associated with failing RHA or ARMD. The specificity of these levels in predicting poor function was high (95%), but the sensitivity was low (25%), which is supported by other studies.[29-31] This makes the follow-up of metal ion levels even more confusing. It implies that clinicians cannot solely rely on metal ion level measurements, as a screening measure for failing MoM prostheses or ARMD. A trend of metal ion levels may be more predictive in for the occurrence of ARMD.

The controversy on the role of metal ion levels in the occurrence of ARMD and failing implants is a result of the fact that the exact pathology of pseudotumour formation is far from fully understood. A toxic reaction to an abundant volume of metal particles, as well as a delayed hypersensitivity reaction to these particles has also been given as a causative factor.[9] With a hypersensitivity reaction, metal ions do not have to be elevated beyond toxic levels in order to cause a soft-tissue reaction. As per the study (Chapter 3), two out of the three revisions for a pseudotumour had relatively low metal ion levels (<2.0 µg/L). The small number of encountered pseudotumours in this study made it impossible to draw any conclusion on an absence of possible correlation between metal ion levels and pseudotumour formation.

5. Defining if concerns on metal ion release after MoM hip arthroplasty can be extrapolated to a metal-on-metal discus arthroplasty in the lumbar spine.

The elevated metal ion levels and the adverse reactions to metal ion debris after a MoM hip arthroplasty raised concerns amongst hip surgeons and led to official alerts and guidelines of medical authorities. These concerns were not extrapolated to other orthopaedic metal-on-metal arthroplasties elsewhere in the body, such as a MoM total disc arthroplasty used in the lumbar spine. A total disc arthroplasty (TDA) is a surgical procedure used to treat degenerative disc disease and some designs use two metal plates that articulate as a ball-in-socket. As in MoM hip arthroplasty, it is conceivable that this MoM articulation can also elicit detectable metal ion concentrations in blood and can led to ARMD. By comparison, very little attention has been paid to this phenomenon in spinal surgery. **Chapter 5** presents a study, in which it is questioned if concerns on elevated metal ion levels in MoM hip arthroplasty should be extended to a MoM TDA used in the lumbar spine.

Metal ion levels in whole blood and serum were analysed in four groups of patients; (1) patients with a TDA of the lumbar spine, (2) RHA, (3) 28-mm diameter MoM THA and (4) a control group without a MoM implant. Metal ion levels were measured in patients with a TDA at a median follow-up of 34.5 and at exactly 12 months for the both hip arthroplasty groups. Metal ion levels in the TDA group were significantly lower than those after resurfacing or MoM THA. Patients with a well-functioning single-level TDA appeared to have cobalt and chromium levels that were in most cases similar to those measured preoperatively in control patients without any form of MoM implant. Only cobalt levels in whole blood showed a significant median increase to 0.6 µg/l after a TDA, which is just above the detection limit of 0.5 µg/l.

The fact that the metal ion levels were remarkably low may suggest that the amount of wear debris from a well-positioned TDA is relatively low. Earlier reports estimated the wear debris from a Maverick TDA to be between 0.38-0.44 mm^3 per year, compared with 1-5 mm^3 for a MoM hip replacement.[32,33] This difference in wear is almost certainly due to the fact that the kinematics of a TDA, such as loading, shear forces, contact area and range of movement,

are profoundly different from those of any hip replacement. The range of movement in a TDA is relatively limited, and the shear forces are rather low, due to the contained position of the device. This will result in lower friction of the articulating surfaces and reduced wear.

In conclusion, there is only limited cause for concern, as in this study the post-operative metal ion levels were significantly lower after TDA than after THA and RHA, and were generally comparable to those the general population. However, since the sensitivity of metal ion analysis in MoM hip arthroplasty is proven to be low and the exact pathology of pseudotumour formation is far from fully understood surgeons should be cautious and screen their patients at regular intervals or in case of complaints.

6. Determining if periprosthetic lesions, as seen on MRI, and classified as pseudotumours are exclusively seen around metal-on-metal hip implants.

The complex interaction between implant and patient related factors makes it hard to find a sensitive and specific screening method for ARMD. Generally, the developed guidelines recommended clinical evaluation, metal ion level determination and cross-sectional imaging such as ultrasound, CT and MRI. Metal ion analysis seems to have high specificity, but low sensitivity.[29-31] For cross-sectional imaging, this is less specified. Cross-sectional imaging of the hip frequently reveals soft-tissue and fluid collections, muscle atrophy and oedema, in relation to MoM joint arthroplasties, mostly classified as pseudotumours. The real significance of the lesions is, nevertheless, uncertain, because identical series on bearings other than metal-on-metal are scarce. It is questionable if all lesions seen on cross-sectional imaging of are actual, destructive pseudotumours, or if a part is actually physiological, and also seen in total hip arthroplasties other than MoM bearings.

Chapter 6 focuses on the prevalence of periprosthetic lesions diagnosed by metal-artefact-reducing sequence-MRI (MARS-MRI) in patients with (1) a RHA, (2) small-diameter MoM THA and (3) an asymptomatic group of patients with a small-diameter ceramic-on-polyethylene (CoP) THA. All depicted lesions were graded by three recognised classification systems for pseudotumours given in literature.

The study presented in Chapter 6 illustrates that periprosthetic lesions seen on MARS-MRI and classified as pseudotumours by currently available scoring systems, are not exclusively seen in MoM hip arthroplasties. Surprisingly, the prevalence of periprosthetic lesions was equally distributed between the RHA (17%) and CoP THA (18%) groups, whereas these lesions were less commonly identified in the MoM THA group (4%). Solid periprosthetic lesions were exclusively seen in the RHA group, while all other lesions were bulging periprosthetic fluid collections. Nevertheless, the three classification systems graded most lesions as a 'pseudotumour' or 'MoM disease' with relatively high grading.

Owing to the similar prevalence of periprosthetic lesions in the RHA and CoP groups, the question arises of whether all identified periprosthetic lesions are 'real' pseudotumours with clinical significance or not. Some fluid collection, in absence of any destructive characteristics, without signs of infection, in patients with good function and without pain, seems to be normal after any kind of THA. This is demonstrated by the fact that despite the high grading on the different MRI classification systems, nine of 13 periprosthetic lesions were small (< 25 ml) fluid collections, in the presence of good clinical results and low metal ion levels. Currently used classification systems seem to overestimate the prevalence of pseudotumours depicted by MARS-MRI. A better MRI classification system is required to reflect clinically relevant pseudotumours, in which a high grade actually corresponds with pathologically- and clinically relevant lesions. The presence of solid lesions, muscle damage and thickened capsule should be emphasised in seeking to define clinically relevant pseudotumours. Furthermore, the size of periprosthetic lesions changes over the course of time.[34] Serial MRI may have an important role in differentiating benign from pathological lesions.

7. A case report of a patient with a destructive pseudotumour in the absence of a metal-on-metal bearing.

The occurrence of ARMD seems to be a multifactorial process. As in these studies, there is no clear relation between metal ion levels and pseudotumour formation (Chapters 3 and 6). These findings are supported by other studies, in which the extent of tissue destruction at revision surgery did not appear to be dose-related to the volumetric wear.[19,35] There seems to be another factor that can be sought in patient-related immunological responses.[11,36] In addition, it is not only the bearing surface that is prone to wear and the products of corrosion. Corrosion and wear can occur at any given MoM junction, when a passive protective oxide film on the metallic surfaces is constantly disrupted by fretting and micro-motion.[37,38] The extent of the corrosion process is affected by a number of factors, including the amount and quality of metallic junctions and forces that are projected on the junctions.[38-40]

In **Chapter 7,** a case report is presented of a patient with a rapidly forming, large and destructive pseudotumour after a THA with a double-mobility metal-on-polyethylene bearing. Serum levels of chromium were below the detection level of 0.5µg/L, whereas cobalt serum levels were 5.7 µg/L. The pseudotumour could only have been triggered by metal ion release from the head-neck taper junction, since no other MoM articulating surface was used. This case report clearly demonstrates that the bearing surface is not the only source of ARMD. As components from different manufacturers were used, a subtle, angular mismatch between the trunnion and taper was created. Consequently, this incongruence may have led to increased wear and corrosion.

Metal ion debris release from the head-neck taper junction is not exclusively seen in cases of mismatch. The release from the taper-head junction also seems to play a major role in the high incidence of ARMD in patients with a large-diameter head (LDH) MoM total hip arthroplasties. Numerous authors have reported higher metal ion levels and incidences of ARMD after LDH MoM THA, than after RHA using otherwise identical bearing characteristics.[41,42] The latter lacks any modular MoM junctions, which may explain the difference encountered. In the presented case, the double-mobility system may have led to greater stresses on the taper junction according to the same principle that applies to LDH

MoM THAs. An increase in head-diameter causes an increased frictional force between the articulating surfaces and increases the length of arm, which may all induce a greater mechanical stress on the head-neck junction. Several reports are now available that explain the extent, to which the taper contributes to the release of corrosion products and ARMD.[43-45]

The reports on higher metal ion levels and incidences of ARMD after LDH MoM THA and the presented case report confirm that not all MoM hip arthroplasties can be 'lumped together' when analysing the incidence or ARMD. It is of great importance to define the brand and type of MoM implant. An RHA, LDH MoM THA (>36 mm diameter) and small-diameter head MoM THA of any given brand has its own characteristics. Prostheses vary in (1) the use of cast or forced material, (2) heat treatment, (3) radial clearance, (4) arc of coverage, and (5) angle of function of the femoral component, that all influence the wear, metal ion release and failure rates.[19] Due to subtle differences of design, some implants seemed to have a very narrow arc of optimal component positioning.[46,47] The acetabular positioning seems to be a particularly important determinant in implant failure rate. A high acetabular inclination is associated with edge-loading (contact between the femoral and acetabular components occurs at the edge/rim of the acetabular component wear) and the occurrence of adverse reactions.[48-51]

Once again, it must be emphasised that all prostheses have their own successes and failures, and surgical technique is a key factor for success. The prostheses used in this study, together with the Birmingham Hip Resurfacing, turned out to be a prosthesis with a rather successful ten-year follow-up.[1,52] The results of this study, therefore, cannot for that reason be extrapolated to all RHAs and small-diameter MoM THAs.

GENERAL DISCUSSION

At the time of its reintroduction, the RHA was extensively promoted as a good alternative to the conventional type of THA for young and active patients due to its stability and wear characteristics. The RHA was assumed to be a new hip implant that would, in contrast to the conventional THA, last a lifetime. This thesis is based on a prospective randomised clinical trial of young patients with an RHA, who were compared to patients with a conventional type of MoM THA.

In conclusion, it can be stated that both groups showed highly satisfied and well-functioning patients, with only some significant differences in clinical score in favour of the RHA group at short to mid-term follow-up. Moreover, the RHA seems to be a proven, mechanically stable concept, with no dislocations during follow-up. However, it can be discussed if these advantages are clinically relevant and if they are worth the risks of elevated metal ion levels and any form of ARMD. In addition, the thesis illustrates the difficulties in interpretation of metal ion analysis, cross-sectional imaging and its classification systems, and difficulties in determination of the source of ARMD.

Once again, it must be emphasised that this thesis focussed on a single brand of RHA (Conserve Plus®, Wright Medical), that appeared to have a relative low frequency of ARMD and rather satisfactory survival.[1,52,53] In addition, operations were carried out by a limited number of experienced hip surgeons, who may have played a role in the relatively good outcome, as it is recognised that the surgical technique is important to obtain a good outcome in hip resurfacing.

National- and international joint registries reveal a clear difference in survival between RHA, MoM LDH THA and THAs of any other bearing combination. The number of revisions of RHA is significantly higher compared to any other kind small-diameter head THA, with a profound difference between men and women. The Dutch Arthroplasty Register (LROI) reported a five-year RHA failure rate of 5.3% for men and 13.5% for women compared to an average of 3.5% and 3% for men and women respectively in any other type of bearing.[1] However, there are several factors that must be taken into account in evaluating

these numbers. Firstly, the adverse reactions to metal-on-metal bearings caused a general, global fear of metal-on-metal implants. Moreover, there were recalls for specific implants. The fear of adverse reactions, and inevitably, the subsequent fear of possible lawsuits, may have resulted in revisions of asymptomatic patients without clinically significant ARMD. Additionally, all types of metal-on-metal implants are often bundled together in the registries. As is known from literature, there are RHAs from specific brands, such as the ASR, that functioned very badly and have a significantly higher reported failure rate.[1,44] Finally, it must be noted that, in general, the RHA was promoted as an alternative for THA in young patients. Consequently, the average age of the patients with an RHA is much lower, as presented in this thesis. Obviously, this patient group has a higher failure rate than compared to the older patient group. The mean age of patients allocated to an RHA in this randomised trial had a mean age of 57.5 years. The reported cumulative, five-years revision percentage was 4.5% for patients in the age category of 50-60 years, which approaches the average revision rate of RHA in men (5.3%) given in the registries.[1] All these aforementioned factors must be taken into account when evaluating joint registries and revision rates of the RHA. Nevertheless, it cannot be denied that all RHA implants, irrespective of type or brand, have their specific reported serious adverse reactions, and the clinical benefit is marginal compared to a conventional type of THA.

The uncertainty about the consequences of elevated metal ion levels, pseudotumour formation and its high failure rate, caused concerns worldwide, and diminished the use and acceptance of MoM bearings[1,52,53] Various medical authorities, such as the UK's Medicines and Healthcare products Regulatory Agency(MHRA), the United States' (US') Food and Drug Administration (FDA), and the Dutch Orthopaedic Association (NOV), have all published medical device alerts and produced guidelines regarding follow-up of patients.[20,28,54] In the Netherlands in 2012, NOV even imposed a (temporary) 'time-out' for the use of all MoM hip implants with heads larger than 36mm, which was only recently postponed.[54] Since the attention was drawn to the potential side-effects of RHA, the initial popularity of the RHA changed drastically, and worldwide, at that time, and turned into concern and disbelief on how these implants could have found their way onto the market.

The initial biomechanical- and clinical successes of the Birmingham Hip Resurfacing (BHR) drew the attention of other manufacturers that wanted to leverage the commercial success of the RHA. Subsequently, most implant manufacturers developed their own MoM implant, each with its own characteristic-based modifications of existing implants. When these MoM implants were introduced, the FDA considered the RHA as a new implant, which had to go through rigorous protocols that required clinical testing. Unlike in the US, the European regulatory bodies judged the implants as a category of device that only requires simulator testing, since the RHA was considered to be an extension of an existing implant design.[55] Although the first reports on elevated metal ion levels and pseudotumours were already present, new RHA implants still found their way to the market. It would appear that regulatory authorities missed a chance to suspend the rapid introduction of RHA implants in the absence of any long term clinical studies.

Illustrated by the failure of the introduction of the RHA, it would appear mandatory that the device regulation and implementation is in need of a change. In the Netherlands, NOV decided to act ahead of this change, and has implemented a plan for the introduction of innovative joint arthroplasties. Implants are now divided into three groups, based on the principles of the National Institute for health and Clinical Excellence (NICE) criteria of the National Health Service (NHS) in the UK; 1A, 1B and 2.[56] Implants with less than a 10% revision rate at a ten-year follow-up are fully accepted and classified as 1A. Those with a revision rate of less than 5% at a five-year follow-up are classified as 1B, and new implants as 2. Use of these implants is only allowed in approved studies. In the UK the Beyond Compliance Service was founded for the latter group of implants.[57] The Beyond Compliance Service consists of an independent panel of experts that works with implant manufacturers and clinicians and collects data about patients who receive a new or modified implants and about their recovery following surgery. This data is used to assess the relative risk of any new or modified product, and the rate at which it should be introduced to the market. Systems like these enhance the transparency towards patients and surgeons, and should prevent the introduction of new implants without a proven good long-term clinical result.

In the Netherlands, the ban of all MoM hip arthroplasties with a head diameter above 36 mm, including the RHA, is also an option, after a consideration of the advantages and potential disadvantages. This decision is a national one, and is rather exceptional worldwide. Despite

the potential disadvantages, the RHA remains an appealing concept for preserving patients' own bone stock and anatomy with a minimal number of dislocations. The improved stability is particularly advantageous for young and active patients, but the risk of ARMD and its subsequent early revisions must be minimised. Perhaps in time, the RHA can be implanted in a controlled setting in designated, specialised hip centres, in the Netherlands, within a specific group of patients, such as men less than 55 years old, with a femoral head size larger than 50 mm, a BMI smaller than 35 kg/m^2, and osteoarthritis as primary diagnosis.[52,58] Prerequisites should include that a specific RHA performs according to the NICE criteria and there should be a better understanding of implant design, patient characteristics that affect the chance of ARMD, and the value of screening methods, such as metal ion analysis and cross-sectional imaging.

Lessons can be learned from the problems related to the current generations of RHA that will hopefully give rise to better innovations in hip arthroplasties and more regulated introductions of novel implants on the market. However, the bone- and natural anatomy preserving characteristics of resurfacing remains an appealing concept for hip replacement options for young and active patients, however, the optimal material from which this should be fabricated has yet to be invented.

REFERENCES

1. No author listed. LROI Rapportage 2007-2011. 2012. https://issuu.com/bladerboek/docs/lroi-rapportage?e=3144185/1050596
2. Brodner W, Bitzan P, Meisinger V, Kaider A, Gottsauner-Wolf F, Kotz R. Serum cobalt levels after metal-on-metal total hip arthroplasty. *J Bone Joint Surg Am* 2003;85-A-11:2168-73.
3. Ladon D, Doherty A, Newson R, Turner J, Bhamra M, Case CP. Changes in metal levels and chromosome aberrations in the peripheral blood of patients after metal-on-metal hip arthroplasty. *J Arthroplasty* 2004;19-8 Suppl 3:78-83.
4. MacDonald SJ. Metal-on-metal total hip arthroplasty: the concerns. *Clin Orthop Relat Res* 2004-429:86-93.
5. Preference Collaborative Review Group. Patients' preferences within randomised trials: systematic review and patient level meta-analysis. *BMJ* 2008-Oct 31:337.
6. Stulberg BN, Fitts SM, Bowen AR, Zadzilka JD. Early return to function after hip resurfacing: is it better than contemporary total hip arthroplasty? *J Arthroplasty* 2010;25-5:748-53.
7. Vendittoli PA, Riviere C, Roy AG, Barry J, Lusignan D, Lavigne M. Metal-on-metal hip resurfacing compared with 28-mm diameter metal-on-metal total hip replacement: a randomised study with six to nine years' follow-up. *Bone Joint J* 2013;95-B-11:1464-73.
8. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. *J Bone Joint Surg Br* 2010;92-1:38-46.
9. Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gibbons CL, Ostlere S, Athanasou N, Gill HS, Murray DW. Pseudotumours associated with metal-on-metal hip resurfacings. *J Bone Joint Surg Br* 2008;90-7:847-51.
10. Park YS, Moon YW, Lim SJ, Yang JM, Ahn G, Choi YL. Early osteolysis following second-generation metal-on-metal hip replacement. *J Bone Joint Surg Am* 2005;87-7:1515-21.
11. Willert HG, Buchhorn GH, Fayyazi A, Flury R, Windler M, Koster G, Lohmann CH. Metal-on-metal bearings and hypersensitivity in patients with artificial hip joints. A clinical and histomorphological study. *J Bone Joint Surg Am* 2005;87-1:28-36.
12. Bisschop R, Boomsma MF, Van Raay JJ, Tiebosch AT, Maas M, Gerritsma CL. High prevalence of pseudotumors in patients with a Birmingham Hip Resurfacing prosthesis: a prospective cohort study of one hundred and twenty-nine patients. *J Bone Joint Surg Am* 2013;95-17:1554-60.

13. Canadian Hip Resurfacing Study Group. A survey on the prevalence of pseudotumors with metal-on-metal hip resurfacing in Canadian academic centers. *J Bone Joint Surg Am* 2011;93 Suppl 2:118-21.
14. Williams DH, Greidanus NV, Masri BA, Duncan CP, Garbuz DS. Prevalence of pseudotumor in asymptomatic patients after metal-on-metal hip arthroplasty. *J Bone Joint Surg Am* 2011;93-23:2164-71.
15. Ebreo D, Bell PJ, Arshad H, Donell ST, Toms A, Nolan JF. Serial magnetic resonance imaging of metal-on-metal total hip replacements. Follow-up of a cohort of 28 mm Ultima TPS THRs. *Bone Joint J* 2013;95-B-8:1035-9.
16. Innmann MM, Gotterbarm T, Kretzer JP, Merle C, Ewerbeck V, Weiss S, Aldinger PR, Streit MR. Minimum ten-year results of a 28-mm metal-on-metal bearing in cementless total hip arthroplasty in patients fifty years of age and younger. *Int Orthop* 2014;38-5:929-34.
17. Kwon YM, Glyn-Jones S, Simpson DJ, Kamali A, McLardy-Smith P, Gill HS, Murray DW. Analysis of wear of retrieved metal-on-metal hip resurfacing implants revised due to pseudotumours. *J Bone Joint Surg Br* 2010;92-3:356-61.
18. De Smet K, De Haan R, Calistri A, Campbell PA, Ebramzadeh E, Pattyn C, Gill HS. Metal ion measurement as a diagnostic tool to identify problems with metal-on-metal hip resurfacing. *J Bone Joint Surg Am* 2008;90 Suppl 4:202-8.
19. Langton DJ, Joyce TJ, Jameson SS, Lord J, Van Orsouw M, Holland JP, Nargol AV, De Smet KA. Adverse reaction to metal debris following hip resurfacing: the influence of component type, orientation and volumetric wear. *J Bone Joint Surg Br* 2011;93-2:164-71.
20. No author listed. Medicines and Healthcare products Regulatory Agency: Medical safety alert: Metal-on-metal (MoM) hip replacements - updated advice with patient follow ups. 2012; https://www.gov.uk /drug-device-alerts/medical-device-alert-metal-on-metal-mom-hip-replacements-updated-advice-with-patient-follow-ups
21. No author listed. Advies Metaal Op Metaal articulerende implantaten (MOM) van de Nederlandse Orthopaedische Vereniging (NOV). 2011; http://www.orthopeden.org/uploads/_z/J2/_zJ20N3vfJO MKW7m3OcWkQ/Nov-Advies-MoM-EINDVERSIE-16-JUNI-2011-tbv-Email-alert.pdf
22. Back DL, Young DA, Shimmin AJ. How do serum cobalt and chromium levels change after metal-on-metal hip resurfacing? *Clin Orthop Relat Res* 2005;438:177-81.

23. Moroni A, Savarino L, Hoque M, Cadossi M, Baldini N. Do ion levels in hip resurfacing differ from metal-on-metal THA at midterm? *Clin Orthop Relat Res* 2011;469-1:180-7.
24. Bradberry SM, Wilkinson JM, Ferner RE. Systemic toxicity related to metal hip prostheses. *Clin Toxicol (Phila)* 2014;52-8:837-47.
25. Triclot P. Metal-on-metal: history, state of the art (2010). *Int Orthop* 2011;35-2:201-6.
26. Ikeda T, Takahashi K, Kabata T, Sakagoshi D, Tomita K, Yamada M. Polyneuropathy caused by cobalt-chromium metallosis after total hip replacement. *Muscle Nerve* 2010;42-1:140-3.
27. Keegan GM, Learmonth ID, Case CP. Orthopaedic metals and their potential toxicity in the arthroplasty patient: A review of current knowledge and future strategies. *J Bone Joint Surg Br* 2007;89-5:567-73.
28. No author listed. U.S. Food and Drug Administration: Metal-on-Metal Hip Implants: FDA Safety Communication. 2013; http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm335775.htm
29. Van Der Straeten C, Grammatopoulos G, Gill HS, Calistri A, Campbell P, De Smet KA. The 2012 Otto Aufranc Award: The interpretation of metal ion levels in unilateral and bilateral hip resurfacing. *Clin Orthop Relat Res* 2013;471-2:377-85.
30. Macnair RD, Wynn-Jones H, Wimhurst JA, Toms A, Cahir J. Metal ion levels not sufficient as a screening measure for adverse reactions in metal-on-metal hip arthroplasties. *J Arthroplasty* 2013;28-1:78-83.
31. Malek IA, King A, Sharma H, Malek S, Lyons K, Jones S, John A. The sensitivity, specificity and predictive values of raised plasma metal ion levels in the diagnosis of adverse reaction to metal debris in symptomatic patients with a metal-on-metal arthroplasty of the hip. *J Bone Joint Surg Br* 2012;94-8:1045-50.
32. Amstutz HC, Campbell P, McKellop H, Schmalzreid TP, Gillespie WJ, Howie D, Jacobs J, Medley J, Merritt K. Metal on metal total hip replacement workshop consensus document. *Clin Orthop Relat Res* 1996-329 Suppl:S297-303.
33. Mathews HH, Lehuec JC, Friesem T, Zdeblick T, Eisermann L. Design rationale and biomechanics of Maverick Total Disc arthroplasty with early clinical results. *Spine J* 2004;4-6 Suppl:268S-75S.
34. Hasegawa M, Miyamoto N, Miyazaki S, Wakabayashi H, Sudo A. Longitudinal magnetic resonance imaging of pseudotumors following metal-on-metal total hip arthroplasty. *J Arthroplasty* 2014;29-12:2236-8.

35. Liow MH, Urish KL, Preffer FI, Nielson GP, Kwon YM. Metal Ion Levels Are Not Correlated With Histopathology of Adverse Local Tissue Reactions in Taper Corrosion of Total Hip Arthroplasty. *J Arthroplasty* 2016.
36. Matthies AK, Skinner JA, Osmani H, Henckel J, Hart AJ. Pseudotumors are common in well-positioned low-wearing metal-on-metal hips. *Clin Orthop Relat Res* 2012;470-7:1895-906.
37. Gilbert JL, Buckley CA, Jacobs JJ. In vivo corrosion of modular hip prosthesis components in mixed and similar metal combinations. The effect of crevice, stress, motion, and alloy coupling. *J Biomed Mater Res* 1993;27-12:1533-44.
38. Jacobs JJ, Gilbert JL, Urban RM. Corrosion of metal orthopaedic implants. *J Bone Joint Surg Am* 1998;80-2:268-82.
39. Brown SA, Flemming CA, Kawalec JS, Placko HE, Vassaux C, Merritt K, Payer JH, Kraay MJ. Fretting corrosion accelerates crevice corrosion of modular hip tapers. *J Appl Biomater* 1995;6-1:19-26.
40. Goldberg JR, Gilbert JL, Jacobs JJ, Bauer TW, Paprosky W, Leurgans S. A multicenter retrieval study of the taper interfaces of modular hip prostheses. *Clin Orthop Relat Res* 2002-401:149-61.
41. Garbuz DS, Tanzer M, Greidanus NV, Masri BA, Duncan CP. The John Charnley Award: Metal-on-metal hip resurfacing versus large-diameter head metal-on-metal total hip arthroplasty: a randomized clinical trial. *Clin Orthop Relat Res* 2010;468-2:318-25.
42. Vendittoli PA, Amzica T, Roy AG, Lusignan D, Girard J, Lavigne M. Metal Ion release with large-diameter metal-on-metal hip arthroplasty. *J Arthroplasty* 2011;26-2:282-8.
43. Hothi HS, Berber R, Whittaker RK, Blunn GW, Skinner JA, Hart AJ. The Relationship Between Cobalt/Chromium Ratios and the High Prevalence of Head-Stem Junction Corrosion in Metal-on-Metal Total Hip Arthroplasty. *J Arthroplasty* 2015.
44. Langton DJ, Jameson SS, Joyce TJ, Gandhi JN, Sidaginamale R, Mereddy P, Lord J, Nargol AV. Accelerating failure rate of the ASR total hip replacement. *J Bone Joint Surg Br* 2011;93-8:1011-6.
45. Cooper HJ, Della Valle CJ, Berger RA, Tetreault M, Paprosky WG, Sporer SM, Jacobs JJ. Corrosion at the head-neck taper as a cause for adverse local tissue reactions after total hip arthroplasty. *J Bone Joint Surg Am* 2012;94-18:1655-61.

46. Langton DJ, Jameson SS, Joyce TJ, Webb J, Nargol AV. The effect of component size and orientation on the concentrations of metal ions after resurfacing arthroplasty of the hip. *J Bone Joint Surg Br* 2008;90-9:1143-51.
47. Amstutz HC, Le Duff MJ, Johnson AJ. Socket position determines hip resurfacing 10-year survivorship. *Clin Orthop Relat Res* 2012;470-11:3127-33.
48. Mellon SJ, Grammatopoulos G, Andersen MS, Pandit HG, Gill HS, Murray DW. Optimal acetabular component orientation estimated using edge-loading and impingement risk in patients with metal-on-metal hip resurfacing arthroplasty. *J Biomech* 2015;48-2:318-23.
49. Grammatopoulos G, Pandit H, Glyn-Jones S, McLardy-Smith P, Gundle R, Whitwell D, Gill HS, Murray DW. Optimal acetabular orientation for hip resurfacing. *J Bone Joint Surg Br* 2010;92-8:1072-8.
50. Le Duff MJ, Johnson AJ, Wassef AJ, Amstutz HC. Does femoral neck to cup impingement affect metal ion levels in hip resurfacing? *Clin Orthop Relat Res* 2014;472-2:489-96.
51. Kwon YM, Mellon SJ, Monk P, Murray DW, Gill HS. In vivo evaluation of edge-loading in metal-on-metal hip resurfacing patients with pseudotumours. *Bone Joint Res* 2012;1-4:42-9.
52. No author listed. Australian Orthopaedic Association National Joint Replacement Registry: Annual report 2015. https://aoanjrr.sahmri.com/documents/10180/217745/Hip%20and%20Knee%20Arthroplasty
53. No author listed. National Joint Registry: 12th Annual report. 2015. http://www.njrcentre.org.uk /njrcentre/Portals/0/Documents/England/Reports/12th%20annual%20report/NJR%20Online%20Annual%20Report%202015.pdf
54. No author listed. Nederlandse Orthopaedische Vereniging: Het gebruik van metaal-op-metaal heupprothese: aangescherpt advies aan de NOV leden. 2012; http://www.orthopeden.org/vereniging/ alerts/alerts/aangescherpt-mom-advies-voor-nov-leden?objectSynopsis=
55. Cohen D. How safe are metal-on-metal hip implants? *BMJ* 2012;344:e1410.
56. No author listed. Nederlandse Orthopaedische Vereniging: Classification Orthopaedic Implants: NOV Total Hip Prosthesis 2016. 2016; http://www.orthopeden.org/uploads/Da/lQ/DalQCgbjD-urmjX_QEChiQ/HIPLIST-NOV-2016.pdf
57. No author listed. Beyond Compliance Service. 2016. http://www.beyondcompliance.org.uk/Home
58. McMinn DJ, Daniel J, Ziaee H, Pradhan C. Indications and results of hip resurfacing. *Int Orthop* 2011;35-2:231-7.

Vendittoli PA, Amzica T, Roy AG,
large-diameter metal-on-metal hip arthrop.
43. Hothi HS, Berber R, Whittaker RK, Blunn GW, S
Cobalt/Chromium Ratios and the High Prevalence o
on-Metal Total Hip Arthroplasty. *J Arthroplasty* 2015.
Langton DJ, Jameson SS, Joyce TJ, Gandhi JN, Sidagina
celerating failure rate of the ASR total hip replaceme
8:10
45. Cooper HJ, Valle CJ, Berger RA, Tetreault M, Papro
Corrosion at the eck taper as a cause for adverse loca
arthroplasty. *J Bone Joi Am* 2012;94-18:1655-61.

CHAPTER 9

Nederlandse samenvatting en discussie

SAMENVATTING EN DISCUSSIE

Artrose van de heup, coxartrose, is een veelvoorkomende aandoening welke het functioneren van mensen ernstig kan beperken. Een totale heupprothese (THP) is een succesvolle behandeling voor patiënten met een eindstadium van coxartrose. Jaarlijks worden er in Nederland ongeveer 28.000 primaire heupprotheses geplaatst en de verwachting is dat dit aantal in de aankomende jaren zal toenemen. Een nadeel van de conventionele metaal-op-polyethyleen of ceramiek-op-polyethyleen articulerende prothese, is dat deze kan luxeren en dat het polyethyleen slijt, wat kan leiden tot loslating en instabiliteit. Met name bij relatief jonge patiënten kan de slijtage van het polyethyleen relatief snel optreden. In een zoektocht naar een duurzame prothese werd een oud concept, de metaal-op-metaal (MoM) heupprothese en in het bijzonder de resurfacing heupprothese (RHP) geherintroduceerd. Door nieuwe bewerkingstechnieken van het metaal, werd verondersteld dat de RHP slijtvast is. Bovendien resulteert de grote kop van de RHP in meer stabiliteit. Deze heupprothese werd derhalve aanbevolen voor jonge, actieve mensen en werd de 'sportheup' genoemd.

Het doel van dit proefschrift is om een objectieve weergave te geven van de klinische resultaten van een metaal-op-metaal (MoM) articulerende RHP welke in een gerandomiseerd onderzoek werd vergeleken met een conventioneel type MoM THP met een 28 mm kop. Verder geeft het proefschrift een beter inzicht in de problematiek die gepaard gaat met MoM heupprothesiologie, waarbij in het bijzonder de verhoogde metaalionen in bloed en de beeldvorming van pseudotumoren op de voorgrond staan. Er zijn zeven doelstellingen geformuleerd. Deze zullen hieronder worden besproken, waarbij de discussie is verdeeld in een deel met klinische resultaten en een deel waarin de screening van verhoogde metaalionen en pseudotumoren centraal staan.

Klinische resultaten

1. Vaststellen of een uitgesproken voorkeur van een patiënt voor een bepaald type prothese effect heeft op de postoperatieve tevredenheid van een patiënt?

In het begin van de jaren 2000 nam de vraag naar RHP's toe. Verschillende producenten van protheses wilden meeliften op de wereldwijde toegenomen vraag en introduceerden versneld een eigen type RHP. Echter, langetermijnresultaten van het overgrote deel van deze 'nieuwe' implantaten ontbrak. Mogelijke nadelen van de RHP's, zoals een complexere operatietechniek, het voorkomen van verhoogde metaalionconcentraties in bloed en pseudotumoren, werden mogelijk niet op tijd erkend. Om de toegevoegde waarde van een RHP te onderzoeken, werd er een gerandomiseerd onderzoek opgezet, waarbij de RHP werd vergeleken met een conventioneel type MoM articulerende THP met een kleine kop (MoM THP).

Er werd voor een opzet van een gerandomiseerde klinische studie (RCT) gekozen om de RHP objectief te vergelijken met een 'gouden standaard'. Echter, het includeren van patiënten voor de gerandomiseerde studie bleek moeizaam. Ten tijde van de inclusie werd de RHP gepromoot als 'sportheup' en een ideale heupprothese voor jonge en actieve mensen. Aan jonge patiënten, die in aanmerking kwamen voor een heupprothese én voldeden aan de inclusiecriteria, werd gevraagd om mee te doen aan de studie. Een groot deel weigerde echter deelname, vanwege een aanzienlijke voorkeur voor een RHP, ondanks dat benoemd werd dat de voorgestelde voordelen niet bewezen waren. Patiënten met een uitgesproken voorkeur voor een RHP, werden geïncludeerd in een cohort met een follow-up identiek aan de RCT. Hierdoor werden er twee studiegroepen gecreëerd, die zich in principe alleen onderscheidde door een aan- of afwezigheid van een expliciete voorkeur voor de RHP. Dit gaf de mogelijkheid om te onderzoeken in hoeverre een uitgesproken voorkeur voor een prothese effect heeft op de klinische resultaten, waaronder tevredenheid.

De resultaten van deze vergelijkende studie staan beschreven in **Hoofdstuk 2**. Zowel de voorkeursgroep als de gerandomiseerde groep scoorden beide postoperatief hoog op tevredenheid en de overige klinische scores. Er was een trend tot een hogere tevredenheid

onder de patiënten in de voorkeursgroep, maar dit verschil was niet statistisch significant. Het enige significante verschil dat kon worden aangetoond, had betrekking op de mentale score van de SF-12. De patiënten in de voorkeursgroep scoorden preoperatief lager dan de patiënten in de gerandomiseerde groep.

Ondanks het feit dat veel clinici te maken hebben met patiënten met een duidelijke voorkeur voor een bepaalde behandeling, is er relatief weinig wetenschappelijk onderzoek verricht naar het effect hiervan op klinische resultaten en patiënttevredenheid. In onze studie konden we geen invloed een uitgesproken voorkeur aantonen. Dit is in tegenspraak met een meta-analyse waarin verondersteld werd dat een voorkeur voor een behandeling een positief effect zou hebben op de resultaten van de behandeling. In dit onderzoek werden echter naast operatieve ook conservatieve behandelingen geïncludeerd, waarbij therapietrouw een rol speelt. Dit is niet van toepassing op de studie beschreven in Hoofdstuk 2, waarbij beide groepen een identieke nabehandeling kregen. Tevens is het besluit om überhaupt een heupprothese te plaatsen voor veel patiënten al bevredigend, wat zich kenmerkt door een hoge patiënttevredenheidscore bij zowel patiënten met zowel een RHP als met een THP.

2. Objectief vergelijken van de klinische resultaten van patiënten met een resurfacing heupprothese en met die van patiënten met een metaal-op-metaal heupprothese met een 28 mm diameter kop na een follow-up van drie tot vijf jaar.

De klinische resultaten van de gerandomiseerde klinische studie, waarin de RHP werd vergeleken met een 28 mm kop MoM THP (MoM THP) na een follow-up van drie tot vijf jaar, staan beschreven in **Hoofdstuk 3**. Eénenzeventig patiënten jonger dan 65 jaar werden geïncludeerd in een periode van juni 2007 tot januari 2010. Na randomisatie werd er bij 38 patiënten een RHP (Conserve® Plus, Wright Medical Technology, Arlington, Tennessee, USA) geplaatst en bij 33 patiënten een MoM THP (Zweymuller® Classic Metasul®, Zimmer Orthopaedics, Warsaw, Indiana, USA). Alle patiënten hadden ten tijde van de analyse een follow-up van 36 maanden en ongeveer 50% had een follow-up van vijf jaar.

De klinische scores verbeterden postoperatief significant in beide groepen ten opzichte van de preoperatieve scores. De Visueel Analoge Schaal (VAS) voor tevredenheid, de

Oxford Hip Score (OHS) en de University of Los Angeles Activity Score (UCLA) waren op verschillende momenten gedurende de follow-up statistisch significant hoger in de RHP groep. Deze significante verschillen verdwenen echter naarmate de follow-up periode langer werd. Over het algemeen kan geconcludeerd worden, dat patiënten in de RHP groep met name in de eerste twee jaar postoperatief het klinisch beter doen dan patiënten met een MoM THP. Na deze periode van twee jaar, kan er geen duidelijk significant verschil tussen de twee groepen meer worden aangetoond. Deze resultaten komen overeen met eerdere soortgelijke studies. Deze studies beschrijven een algemene tendens dat patiënten met een RHP het klinisch net wat beter doen dan patiënten met een conventionele heupprothese, maar dat de significante verschillen verdwijnen op lange termijn.

Wat betreft de overlevingsduur van de protheses, kan worden gesteld, dat na vijf jaar follow-up er zes heupprotheses zijn gereviseerd; drie in de RHA groep (8%) en drie in de MoM THP groep (9%). Gedurende de eerste twee jaar van de follow-up waren er twee patiënten in de MoM THP groep, waarbij er een insert wissel had plaatsgevonden in verband met recidiverende luxaties. Bij één patiënt met een RHP werd de femorale component gereviseerd in verband met aseptische loslating bij avasculaire necrose.

De overige drie revisies, na de eerste twee jaar follow-up, waren allen gerelateerd aan 'Adverse Reactions to Metal Debris' (ARMD). Rond deze periode verschenen er meerdere publicaties over ARMD na plaatsing van MoM articulerende heupprotheses. ARMD is een overkoepelende term voor diverse reacties die kunnen optreden na MoM prothesiologie, zoals overgevoeligheid, osteolyse en vocht-bevattende of solide pseudotumoren. De prevalentie van pseudotumoren beschreven in de literatuur varieert van 0,1% tot 67%, met een tendens van een toenemende prevalentie in de loop der jaren. Vanwege de beschreven prevalentie werd er in onze studiepopulatie een hoge prevalentie van ARMD na de eerste twee jaar follow-up verwacht, maar dit bleek niet het geval (Hoofdstuk 3). Na drie jaar follow-up werden er drie pseudotumoren vastgesteld; twee in de RHP groep en één in de MoM THP groep. Deze pseudotumoren waren allen symptomatisch en de heupprotheses werden derhalve gereviseerd. Het optreden van een pseudotumor in de MoM THP groep is redelijk opmerkelijk te noemen. Pseudotumoren worden in de literatuur zelden beschreven bij patiënten met een kleine diameter kop MoM THP. Er zijn twee studies die een prevalentie van 0,5-1,8% beschrijven bij een 28 mm kop MoM THP in een periode van een 10-jaars follow-up. Dit getal ligt beduidend lager dan de 3% beschreven in Hoofdstuk 3.

De prevalentie van pseudotumoren in de RHP groep (5%) kan als relatief laag worden beschouwd, vergeleken met de prevalenties beschreven in de literatuur die tot wel 67% gaan. Echter, het moet wel opgemerkt worden dat een cross-sectioneel beeldvormend onderzoek geen onderdeel was van de studie beschreven in Hoofdstuk 3. Cross-sectioneel onderzoek werd wel in een latere fase verricht en staat beschreven in Hoofdstuk 6.

De werkelijke incidentie, pathogenese en klinische relevantie van ARMD blijft tot op de dag van vandaag tot op zekere hoogte onduidelijk. Deze onzekerheid wordt veroorzaakt door een breed scala aan factoren, welke worden geassocieerd met het optreden van ARMD, zoals slijtage, het ontwerp en formaat van het implantaat, de accurate plaatsing van de prothese, maar ook patiënt-specifieke factoren zoals overgevoeligheid. Bovendien ontbreekt er ook nog een éénduidige definitie van een pseudotumor. Dit alles te samen maakt dat de beschreven prevalentie van pseudotumoren sterk uiteen kan lopen.

Screening voor 'Adverse Reactions to Metal Debris'

Nadat er verscheidene studies het optreden van AMRD na plaatsing van een MoM prothese rapporteerden, werden er wereldwijd verschillende richtlijnen ontwikkeld voor het opvolgen van patiënten met een dergelijke prothese. Deze richtlijnen adviseerden een regelmatige controle met daarbij gedegen lichamelijk onderzoek, het bepalen van metaalionconcentraties in bloed en aanvullende beeldvorming in de vorm van echo, CT of MRI. De metaalionconcentratie-bepalingen worden geadviseerd nadat er studies verschenen, waarin verhoogde metaalionconcentraties werden gecorreleerd met het ontstaan van pseudotumoren. Daarnaast werden er ook een relaties beschreven tussen verhoogde metaalionconcentraties en slijtage en de functie van een MoM heupprothese. Derhalve werden metaalionconcentraties gezien als een adequate manier om patiënten met een MoM prothese te vervolgen.

De metaalionconcentraties kunnen bepaald worden in urine, bloed en serum. Aangezien voor de bepaling in urine een 24-uurs collectie noodzakelijk is en dit mede afhankelijk is van hydratietoestand van de patiënt, is deze methode minder aantrekkelijk dan de bepalingen in bloed. Metaalionconcentraties in bloed en serum werden in het eerder beschreven gerandomiseerde onderzoek (Hoofdstuk 3) tijdens vaste tijdstippen bepaald bij alle geïncludeerde patiënten.

3. Vaststellen van het verschil in metaalionconcentraties tussen patiënten met een resurfacing heupprothese en patiënten met een 28 mm kop metaal-op-metaal totale heupprothese.

De resultaten van een prospectief onderzoek, waarbij kobalt- en chroomionenspiegels in bloed en serum werden bepaald bij zowel patiënten met een RHP als een MoM THP, staan beschreven in **Hoofdstuk 3**. In beide groepen is er een duidelijke toename van kobalt en chroom ionenspiegels gedurende een 'running-in' fase van één jaar en stabilisatie (kobalt) of afname (chroom) nadien. Onafhankelijk van het type prothese bleven de mediane waardes onder de door de Nederlandse Orthopaeden Vereniging (NOV) gedefinieerde grenswaarde van 2,0 µg/l en ver beneden de grenswaarde gedefinieerd door de United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) (kobalt 119 nmol/l = 7,0 µg/l; chromium 134,5 nmol/l = 7,0 µg/l). De metaalionconcentraties in bloed en serum in patiënten met een RHP, zijn over het geheel gezien hoger dan die van patiënten met een MoM THP. Dit verschil werd kleiner gedurende de follow-up door een daling van de metaalionconcentraties in de RHP groep. De beschreven metaalionconcentraties zijn relatief laag in vergelijking met andere studies. Dit kan het beste verklaard worden door het type prothese dat in de studie werd gebruikt in combinatie met een adequate plaatsing.

4. Bepalen of metaalionconcentraties in bloed en serum uitwisselbaar zijn, of dat een formule een betrouwbare conversie van serum naar bloed kan weergeven.

Daar waar metaalionconcentraties worden beschouwd als indicator voor slijtage en het functioneren van een prothese, is het van belang dat orthopedische chirurgen de concentraties ook kunnen interpreteren. Dit wordt echter bemoeilijkt door een gebrek aan consensus over de superioriteit van bepalingen in serum of bloed. Daarnaast wordt niet altijd benoemd of de gegeven grenswaarden in serum of bloed zijn. Aangezien de concentraties in bloed en serum van elkaar verschillen, is het van belang om te bepalen of deze waardes door elkaar heen gebruikt mogen worden.

In **Hoofdstuk 4** wordt er een analyse beschreven, waarbij bepaald is of metaalionconcentraties gemeten in bloed en serum uitwisselbaarheid zijn. Tevens is er gekeken of er een betrouwbare formule gegeven kan worden voor de conversie van serum- naar bloedconcentraties. Voor dit onderzoek werden de patiënten van het cohort met daarin de patiënten met een uitgesproken voorkeur voor een RHP (beschreven onder stelling 1) gecombineerd met de patiënten uit het gerandomiseerde onderzoek (eveneens onder stelling 1 beschreven). Door deze combinatie ontstonden er twee groepen van 60 patiënten met een RHP en 32 met een MoM THP. In totaal waren er van deze patiënten 343 serum- en bloedmonsters aanwezig voor analyse. De gemiddelde kobalt serumconcentraties waren minimaal lager of gelijk aan de bloedwaardes, wat wordt weergegeven door een gemiddeld verschil van +0,13 µg/l (95%-CI: 0,03;0,22). Het tegenovergestelde geldt voor chroom, waarbij de serumconcentraties gemiddeld hoger waren dan die gemeten in bloed met een gemiddelde van -0,91 µg/l (95%-CI: -1,05;-0,77). Een Bland-Altman plot werd gebruikt om de spreidingsgrenzen te bepalen. Deze grenzen lagen met +1,5 µg/l en -1,25 µg/l voor kobalt en +0,95 µg/L en -2,85 µg/l voor chroom ver uiteen. Hieruit kan geconcludeerd worden dat serum en bloedconcentraties niet uitwisselbaar zijn.

Formules voor de conversie van metaalionconcentraties in bloed naar serum werden gegenereerd vanuit de beschikbare data.

*Kobalt in bloed = 0,34 + (0,88*kobalt in serum)*
*Chroom in bloed = 0,14 + (0,58*chroom in serum)*.

De formules kunnen niet getest worden op de data waaruit deze gegenereerd zijn. Derhalve werd er een nieuwe formule gegenereerd vanuit één helft van de beschikbare data en getest op het andere deel van de data. De Bland-Altman plot werd wederom gebruikt om de foutmarge van de gegeven formules te berekenen. De foutmarge werd berekend op +0,77 µg/l en -0,84 µg/l voor kobalt en +0,92 en -0,98 µg/l voor chroom. Hierbij kan worden aangenomen dat de foutmarge van de formule binnen de 1,0 µg/l valt. Hierbij moet wel de kanttekening worden geplaatst, dat ondanks het splitten van de data de formule vanuit een relatief homogene groep is verkregen. Verificatie op een meer heterogene groep is van belang.

Op basis van onze data kan er geen goede aanbeveling worden gegeven of het gebruik van serum- of bloedbepalingen de voorkeur geniet. Praktisch gezien kan er gesteld worden dat de bepalingen in bloed de voorkeur geniet aangezien deze geen bewerking voor de analyse vereist, wat de kans op contaminatie en daarmee de kans op een foutief hoge uitslag reduceert.

Naast contaminatie is het bij het beoordelen van metaalionconcentraties van belang om implantaat-gerelateerde en patiënt-specifieke factoren zoals nierfunctie, de aanwezigheid van andere metalen implantaten, voedingssupplementen, medicatie en omgevingsfactoren te evalueren. Al deze factoren moeten in ogenschouw genomen worden bij de beoordeling van hoge metaalionconcentraties.

Verhoogde metaalionconcentraties kunnen toxiciteit geven. Carcinogeniteit, overgevoeligheidsreacties, cardiomyopathie, neurologische schade, hypothyreoïdie, nierfunctiestoornissen en veranderingen in psychologische status worden allen genoemd als potentieel effect, maar solide epidemiologische studies die dit bevestigen ontbreken.

Ongeacht de nog aanwezige onzekerheden over verhoogde metaalionconcentraties en hun klinische invloed, is het voor de klinische praktijk van belang grenswaardes van metaalionconcentraties te definiëren. Er is echter geen internationale consensus over de bovengrens van te accepteren metaalionconcentraties. Verschillende nationale- en internationale instanties ontwikkelden elk een eigen richtlijn met grenswaardes. Zo stelde de MHRA voor zowel kobalt als chroom een bovengrens van 7,0 µg/l. De NOV stelt dat een serumwaarde tot 2,0 µg/l veilig is en adviseert een intensieve controles bij een waarde van tussen de 2,0-5,0 µg/l. Deze waardes zijn echter grotendeels gebaseerd op studies die de relatie tussen het functioneren van de prothese en metaalionconcentraties onderzochten, niet de toxiciteit. Een voorbeeld hiervan is de studie van Van der Straeten et al. waarbij er lagere metaalionconcentraties werden gemeten bij patiënten met een goed functionerende prothese, in tegenstelling tot patiënten met een disfunctionerende prothese. De grenswaarde voor het omslagpunt voor unilaterale protheses in serum werd bepaald op 4,6 µg/l en 4,0 µg/l voor respectievelijk chroom en kobalt. Waardes boven deze grens werden geassocieerd met disfunctioneren van de prothese en ARMD met een hoge specificiteit van 95%, maar een zeer lage sensibiliteit (25%). Dit maakt de waarde van metaalionbepalingen in serum

en bloed discutabel. Een trend van metaalionconcentraties lijkt van grotere waarde bij het voorspellen van het optreden van ARMD.

De onduidelijke rol van metaalionconcentraties bij het ontstaan van ARMD en het falen van MoM protheses, is het resultaat van een tot nu toe nog onduidelijke pathologie van ARMD. Gesuggereerde causale factoren zijn een toxische reactie op een grote hoeveelheid metaalpartikels en een overgevoeligheidsreactie voor metaal. In het laatste geval kan een niet-toxische waarde van metaalionen of een kleine hoeveelheid metaalpartikels al ARMD initiëren. Dit komt overeen met een relatief lage metaalionconcentratie (<2,0 µg/L) bij twee van de drie patiënten met een pseudotumor beschreven in Hoofdstuk 3. Het lage aantal pseudotumoren in deze studie maakt het echter onmogelijk om te concluderen dat er geen relatie aanwezig is tussen het ontstaan van pseudotumoren en metaalionconcentraties.

5. Beoordelen of de zorgen om rondom verhoogde metaalionconcentraties na MoM heupprothesiologie geëxtrapoleerd kunnen worden naar MoM discus prothesiologie van de rug.

De verhoogde metaalionconcentraties in bloed en het ontstaan van ARMD na plaatsing van de MoM heupprothese leidde tot veel onrust en zorgen onder heup-orthopeden. Wereldwijd werden er waarschuwingen afgekondigd en werden richtlijnen opgesteld door regelgevende instanties en beroepsverenigingen. Deze waren allen gericht op heupprothesiologie. Andere MoM protheses, zoals bijvoorbeeld een MoM totale discus prothese (TDP) werden hierin niet genoemd. Een TDP wordt gebruikt bij degeneratieve rugklachten en een aantal types TDP's bestaan uit twee metalen plaatjes die als een 'ball-in-socket' articuleren. Het is denkbaar dat, bij een dergelijke prothese, metaalionconcentraties in het bloed ook verhoogd kunnen zijn en er eveneens ARMD kan optreden. **Hoofdstuk 5** beschrijft een studie waarin wordt onderzocht of de zorg rondom MoM-problematiek bij heupprothesiologie uitgebreid moet worden naar andere MoM prothesiologie; in dit geval een MoM TDP.

Kobalt- en chroomconcentraties in bloed en serum van patiënten met een TDP werden vergeleken met die van patiënten met een MoM heupprothese. De studie bestaat uit vier

groepen: (1) patiënten met een MoM TDP, (2) RHP, (3) een 28 mm MoM THA en (4) een controlegroep van patiënten zonder MoM prothese. De metaalionconcentraties in de TDP groep waren significant lager dan die in de twee groepen met heupprotheses. Patiënten met een goed functionerende TDP op één niveau hadden over het algemeen metaalionconcentraties overeenkomstig met die van de controlegroep. Alleen kobaltconcentraties in bloed in de groep met een TDP waren statistisch significant verhoogd met een mediaan van 0,6 µg/l, wat maar net boven de detectiegrens van 0,5 µg/l ligt.

De lage metaalionconcentraties in bloed en serum van patiënten met een goed functionerende TDP suggereren dat de slijtage van een dergelijke prothese relatief laag is. Een eerdere studie schatte de slijtage van de TDP tussen de 0,38-0,44 mm^3/jaar in, vergeleken met 1-5 mm^3 voor een MoM heupprothese. Het kan verondersteld worden dat dit gerelateerd is aan een andere biomechanica. Zo is de bewegingsuitslag van een TDP redelijk beperkt en staat een TDP minder bloot aan grote krachten vergeleken met een heupprothese. Hierdoor zal de slijtage van een TDP lager zijn, wat een aannemelijke verklaring is voor de lage metaalionconcentraties.

Concluderend kan er gesteld worden dat deze studie geen reden geeft voor het uitbreiden van de zorgen rondom de MoM heupprothesiologie problematiek naar andere MoM prothesiologie. Echter, zoals eerder gesteld, is de sensitiviteit van metaalionconcentratie bepalingen voor het voorspellen van ARMD laag. Tevens blijft de exacte pathologie van ARMD onduidelijk. Derhalve valt het aan te bevelen om alle patiënten met een MoM nauwlettend op te volgen en te screenen op ARMD.

6. Bepalen of periprosthetische laesies of pseudotumoren, zoals die op MRI gezien worden bij patiënten met een MoM heupprothese, ook gezien worden bij keramiek-op-polyethyleen heupprothesiologie.

De complexe interactie tussen prothese en patiënt-gerelateerde factoren bemoeilijkt de zoektocht naar een sensitieve en specifieke screeningsmethode voor ARMD. Over het algemeen adviseren de richtlijnen voor screening van patiënten met MoM heupprothese

een gedegen lichamelijk onderzoek, metaalionconcentratie-bepalingen en aanvullende beeldvorming zoals echo, CT of MRI. De sensitiviteit van deze aanvullende onderzoeken is minder goed gespecificeerd vergeleken met metaalionconcentratie-bepalingen. Meerdere onderzoeken beschrijven vocht- en weke delencollecties, spieratrofie en oedeem op MRI na een MoM heupprothese. De vocht- en weke delencollecties worden over het algemeen geclassificeerd als pseudotumor (vorm van ARMD). De werkelijke klinische relevantie van deze bevindingen is echter nog onbekend, aangezien studies naar materialen anders dan MoM erg schaars zijn. De vraag is of alle vocht- en weke delencollecties rondom MoM heupprotheses destructieve pseudotumoren zijn en of een deel niet past bij een normaal beloop na heupprothesiologie en dus ook bij heupprotheses voorkomen met andere articulerende materialen. **Hoofdstuk 6** richt zich op deze vraagstelling. De beschreven studie onderzoekt de prevalentie van periprosthetische laesies, gediagnostiseerd middels metal-artefact-reducing-sequence-MRI (MARS-MRI), bij patiënten met: (1) een RHP, (2) een 28 mm MoM THP en (3) een groep van asymptomatische patiënten met een keramiek-op-polyethyleen articulerende THP (CoP THP). Alle gediagnosticeerde periprosthetische laesies werden gegradeerd volgens drie gepubliceerde classificatiesystemen.

De studie laat zien dat periprosthetische laesies, gediagnosticeerd middels MRI en gegradeerd als pseudotumor middels de drie classificatiesystemen, niet exclusief bij MoM heupprothesiologie voorkomen. Verrassend genoeg was de prevalentie van periprosthetische laesies in de RHP groep (17%) identiek aan die van de CoP THP groep (18%). De prevalentie was het laagst in de groep met een MoM THP (4%). Hierbij moet wel worden opgemerkt dat solide periprosthetische laesies alleen in de RHP groep werden aangetoond. De overige laesies waren vochtcollecties. De gebruikte classificatiesystemen gradeerde deze vochtcollecties echter relatief hoog op de beschreven schaal als pseudotumor.

Gezien de vergelijkbare prevalentie van periprosthetische laesies in de RHP en de CoP THP groep, kan bediscussieerd worden of al deze gediagnosticeerde laesies wel 'echte' klinisch relevante pseudotumoren zijn. Het lijkt er op dat enig vocht rondom een heupprothese bij afwezigheid van klachten, tekenen van infectie en zonder destructief karakter op MRI, een 'normaal' verschijnsel is. Illustratief hiervoor is dat negen van de 13 patiënten met een periprosthetische laesie een kleine vochtcollectie (<25ml), een goede functie van de

prothese en lage metaalionconcentraties in bloed hadden. De huidige classificatiesystemen lijken de prevalentie van pseudotumoren te overschatten. Een beter classificatiesysteem is nodig om klinisch relevante pseudotumoren goed te graderen. De aanwezigheid van een solide laesie, spierschade en een verdikt kapsel moeten hierbij meer aandacht krijgen. Daarnaast lijkt de verandering van de omvang van periprosthetische laesies in verloop van tijd ook een grote rol te spelen bij de differentiatie tussen benigne en pathologische laesies.

7. Beschrijven van een casus van een patiënt met een destructieve pseudotumor in de afwezigheid van een MoM heupprothese.

Het ontstaan van ARMD na een MoM heupprothese lijkt een multifactorieel proces. Zoals in Hoofdstuk 3 en 6 beschreven, is er geen sterke relatie tussen het ontstaan van pseudotumoren en slijtage van de articulerende oppervlaktes of metaalionconcentraties in bloed. Mogelijk is er nog een patiënt-gerelateerde factor, waarbij in de hoek van een immunologische respons gezocht kan worden. Daarnaast ligt de focus op de relatie tussen slijtage van de articulerende oppervlaktes en het ontstaan van pseudotumoren, maar in feite staat elke metalen verbinding bloot aan corrosie en slijtage indien de passieve beschermende oxidelaag beschadigd raakt door bijvoorbeeld microbewegingen. De mate van corrosie wordt daarbij beïnvloed door de kwaliteit van en de hoeveelheid verbindingen en de krachten waaraan de verbinding wordt blootgesteld.

Hoofdstuk 7 beschrijft een casus van een patiënt met een snel vormende, grote, destructieve, solide pseudotumor na een double-mobility metaal-op-polyethylene (MoP) THP. De metaalionconcentraties in serum waren voor chroom onder de detectiegrens van 0,5 µg/l, maar die van kobalt was verhoogd met een waarde van 5,7 µg/l. De pseudotumor werd naar alle waarschijnlijkheid getriggerd door een kleine hoeveelheid metaaldebris vanuit de kop-nek taper verbinding gezien de afwezigheid van een MoM articulerend oppervlak. Dit werd versterkt door een mismatch van kop en steel van verschillende fabrikanten. Echter, ARMD wordt ook beschreven vanuit een kop-nek taper in afwezigheid van een mismatch. De kop-nek taper verbinding lijkt een grotere rol spelen bij het ontstaan van ARMD dan lang werd aangenomen. De kop-nek taper verbinding lijkt namelijk ook een grote rol te spelen

bij de hoge incidentie van AMRD in patiënten met een grote-diameter-kop (LDH, > 36-mm diameter) MoM THP. Verschillende studies tonen een hogere incidentie van ARMD aan bij LDH-MoM THP vergeleken met een RHP met identieke biomechanische kenmerken. Het enige verschil tussen deze protheses zit in de afwezigheid van een kop-nek taper verbinding. In de gepresenteerde casus is er een double-mobility systeem gebruikt, wat biomechanisch overeenkomt met een LDH-MoM THP. Door de grote kop ontstaat er een grotere momentarm en een grotere frictiekracht tussen de articulerende oppervlakten. Dit principe van het ontstaan van ARMD in patiënten met een LDH-MoM THP wordt inmiddels door meerdere studies ondersteund.

De gepresenteerde casus en de rapportages van een hogere incidentie van ARMD in patiënten met een MoM LDH THP, illustreren dat niet alle MoM protheses op één hoop gegooid kunnen worden bij de analyse naar ARMD. Het is hierbij van belang om het type prothese en de fabrikant te definiëren. Een RHP, LDH-MoM THP en een MoM THP met een kleine kop van elke gegeven fabrikant, heeft zijn eigen karakteristieken. De protheses verschillen in (1) gegoten of gesmeed materiaal, (2) wijze van hittebehandelingen, (3) de afstand tussen de articulerende oppervlakten (radial clearance), (4) de mate van overhuiving van het femorale component door het acetabulum en (5) de functionele hoek van de femorale component. Deze kenmerken beïnvloeden allen de mate van slijtage, metaalionconcentraties, incidentie van ARMD en falen van een prothese. Door subtiele verschillen in protheses bleken enkele protheses een zeer kleine marge van optimale implantaat positionering te hebben. Met name de acetabulaire component is hierbij van belang.

Het moet benadrukt worden dat elke protheses zijn eigen successen en beperkingen kent, en niet te vergeten, de chirurgische techniek is ook zeker van cruciaal belang. De protheses die in de onderzoeken voor dit proefschrift zijn gebruikt, bleken een relatief gunstige tien-jaarsoverleving te hebben met een relatief lage incidentie van ARMD. De resultaten, zoals in de gepresenteerde studies, zijn daarom ook niet te extrapoleren naar alle RHP en MoM THPs.

ALGEMENE DISCUSSIE

Ten tijde van zijn herintroductie werd de RHP sterk gepromoot als een goed alternatief voor de 'klassieke' heupprothese en aanbevolen aan jonge en actieve patiënten vanwege de stabiliteit. Tevens zou de RHP door nieuwe bewerkingstechnieken van het metaal slijtvast zijn. De prothese werd daarom, in tegenstelling tot de 'klassieke' heupprothese, gezien als een prothese welke levenslang mee zou kunnen gaan. Het doel van dit proefschrift is om een objectieve weergave te geven van de klinische resultaten van een MoM articulerende RHP welke in een gerandomiseerd onderzoek werd vergeleken met een 28 mm kop MoM THP. Verder geeft het proefschrift een beter inzicht in de problematiek welke gepaard gaat met MoM heupprothesiologie, waarbij in het bijzonder de verhoogde metaalionconcentraties gemeten in bloed en de beeldvorming van pseudotumoren op de voorgrond staan.

Concluderend kan men stellen dat zowel de patiënten met een MoM THP als de patiënten met een RHP zeer tevreden zijn en beide klinisch goed functioneren. Alleen op korte termijn scoren patiënten met een RHP significant beter op een aantal klinische scorelijsten. Daarnaast is de RHP bewezen stabieler met geen enkele luxatie gedurende de gehele studie. Het is echter discutabel of deze voordelen opwegen tegen het risico van ARMD. Dit proefschrift illustreert dat de interpretatie van screeningsmethoden voor ARMD, zoals metaalionbepalingen in bloed en aanvullende beeldvorming in de vorm van een MARS-MRI, complex is.

In de beschouwing van de resultaten, is het wel van belang om te beseffen dat de onderzoeken zijn gebaseerd op één type RHP (Conserve Plus®, Wright Medical). Op lange termijn bleek deze prothese, in tegenstelling tot enkele andere merken RHP's, een relatief goede survival en een lage incidentie van ARMD te kennen. Daarnaast werden de operaties uitgevoerd door ervaren heupchirurgen, wat tevens een rol kan spelen bij de goede klinisch resultaten.

Nationale en internationale implantaten registers tonen een duidelijk verschil in survival tussen RHP, MoM LDH en THP's die gebruik maken van andere articulerende materialen. Het aantal revisies van RHP's is significant hoger dan die van een conventionele kleine-diameter kop (SDH) THP, waarbij het revisiepercentage van RHP's met name bij vrouwen

hoog is. De Nederlandse Landelijke Registratie Orthopedische Implantaten (LROI) rapporteerde voor alle RHP's een gemiddeld vijf-jaars revisiepercentage van 5,3% voor mannen en 13,5% voor vrouwen, vergeleken met een gemiddelde van respectievelijk 3,5% en 3% voor alle conventionele heupprotheses. Het is echter wel van belang om een aantal punten in ogenschouw te nemen bij het beoordelen van deze getallen. Als eerste ligt het revisiepercentage van RHP mogelijk hoger door een algemene angst voor MoM protheses. De enorme negatieve aandacht en de dreiging van rechtszaken hebben mogelijk geleid tot vroege, onnodige revisies van MoM protheses. Daarnaast gaat het om een gemiddelde van alle merken RHPs. Zoals bekend zijn er specifieke merken RHP's zoals de ASR heupprothese, die erg slecht functioneerden en een erg hoog revisiepercentage vertoonden. Deze getallen worden in veel registers geïncludeerd wat kan leiden tot een vertekend beeld. Als laatste is het ook van belang om naar de gemiddelde leeftijd van de patiënten te kijken. De RHP werd gepromoot als een goed alternatief voor met name jonge patiënten. Dit resulteerde in een lagere gemiddelde leeftijd voor deze populatie, zoals ook in de studies geïncludeerd in dit proefschrift (gemiddelde leeftijd 58 jaar). Een lagere leeftijd brengt een hoger revisiepercentage met zich mee. Het geregistreerde vijf-jaars revisiepercentage van THP voor patiënten in de categorie van 50-60 jaar is 4,5%, wat de eerder beschreven 5,3% voor mannen met een RHP nadert. Het algehele revisiepercentage van RHP blijft hoger dan het percentage van de 'conventionele' prothese, maar de genoemde punten nuanceren het enorme verschil. Desalniettemin kan het niet ontkent worden dat RHP ongeacht welke fabrikant dan ook, vervelende complicaties onder de noemer ARMD kan geven. Gegeven de marginaal betere vroege klinische resultaten, kan bediscussieerd worden of de RHP ten opzichte van een 'conventionele' THP een toegevoegde waarde heeft.

De onzekerheden omtrent de gevolgen van verhoogde metaalionconcentraties, pseudotumorformatie en hoge revisiepercentages, maken dat het gebruik van de RHP en de acceptatie van MoM heupprotheses wereldwijd afneemt. Verschillende regulerende instanties, zoals de UK's Medicines and Healthcare products Regulatory Agency (MHRA), de Amerikaanse Food and Drug Administration (FDA) en de Nederlandse Orthopaedische Vereniging (NOV), hebben allen waarschuwingen gepubliceerd en richtlijnen voor follow-up van patiënten met een MoM prothese opgesteld. In Nederland is er zelfs een tijdelijk time-out voor MoM heupprotheses met een kop groter dan 36 mm ingesteld, welke recent werd verlengd.

Het geloof in en de ongekende populariteit van de prothese is wereldwijd afgenomen en heeft plaats gemaakt voor ongeloof en zorgen over hoe een dergelijk implantaat zijn weg naar de markt vond.

Ten tijden van de herintroductie werd de aandacht getrokken door de goede biomechanische en klinische resultaten van de Birmingham Hip Resurfacing (BHR). Andere fabrikanten wilden meeliften op het commerciële effect, wat resulteerde in een wildgroei van RHP's, welke waren gebaseerd op modificaties van bestaande implantaten. De FDA beschouwden deze prothese als een nieuw concept, maar de Europese regulerende autoriteiten zagen het nieuwe concept daarentegen als een kleine variatie op een bestaand product. Dit had als consequentie dat de protheses enkel werden blootgesteld aan een simulatietest. Dit proces, waarbij lange termijn klinische studies ontbreken, heeft een cruciale rol gespeeld in de introductie van verschillende disfunctionerende implantaten op de markt en continueerde ondanks het feit dat de eerste publicaties over ARMD al reeds verschenen.

De gebrekkige testen rondom de introductie van RHP en andere MoM implantaten, illustreert dat de regulatie van implantaten herzien moet worden. De NOV heeft hierop geanticipeerd en heeft een plan geïmplementeerd waarin protheses in drie groepen worden verdeeld. De indeling is gebaseerd op de principes van 'The National Institute for Health and Clinical Excellence' (NICE) criteria van de 'National Health Service' (NHS) in de UK; 1A, 1B en 2. Implantaten met een revisiepercentage lager dan 10% na 10 jaar follow-up worden geclassificeerd als 1A, bij een percentage van 5% na vijf jaar follow-up 1B en nieuwe implantaten worden geclassificeerd als 2. De laatste groep mag alleen in studieverband geïmplanteerd worden. In de UK bestaat er voor deze laatste groep de 'Beyond Compliance Service'. Deze nationale service wordt aangestuurd door een groep onafhankelijke experts die met fabrikanten en orthopeden samenwerken en gegevens en resultaten verzamelen van nieuwe of aangepaste implantaten. Uit deze data kan een risicoanalyse gegenereerd worden en kunnen adviezen gegeven worden over de introductie op markt. Deze genoemde systemen vergroten de transparantie voor zowel patiënt als chirurg en moet voorkomen dat er implantaten worden gebruikt waarvan geen lange termijn gegevens bekend zijn.

De 'tijdelijke' time-out in Nederland van alle MoM heupprothesiologie met een kop groter dan 36 mm is een nationale beslissing na het afwegen van voor- en nadelen. Het is echter

wel een rigoureuze beslissing en wereldwijd relatief uniek. De RHP blijft, ondanks zijn tekortkomingen, een goed concept waarbij zoveel mogelijk van de anatomie behouden blijft en de prothese bewezen stabiel is. De stabiliteit is zeker voor de jonge en actieve patiëntenpopulatie aantrekkelijk. Mogelijk zal er in de toekomst nog plaats komen voor het resurfacing concept. Patiëntenselectie zal hierbij van belang zijn, daar waar jonge mannen onder de 55 jaar, met een diameter kop groter dan 50 mm en een BMI lager dan 35 kg/m^2 en artrose als primaire diagnose relatief goede klinische resultaten laten zien. Voorwaardes hiervoor zijn dat de RHA voldoet aan de NICE criteria, er een betere pathofysiologische kennis over ARMD aanwezig is en de waarde van screeningsmethoden, zoals metaalionbepalingen en beeldvorming bekend zijn.

Er kan lering getrokken worden uit de problemen die gerelateerd zijn aan de invoering van de huidige generatie RHP, wat hopelijk zal leiden tot betere innovaties in de heupprothesiologie en meer gereguleerde introducties van nieuwe implantaten op de markt. Het concept van een RHP, met behoud van originele anatomie blijft een aantrekkelijk concept voor jonge patiënten, echter, het geschikte materiaal waarvan deze gefabriceerd moet worden zal waarschijnlijk nog ontwikkeld moeten worden.

Dankwoord

List of publications

Curriculum Vitae

DANKWOORD

Na velen jaren in de vrije uren werken is het proefschrift dan een feit. Er zijn vele mensen geweest die gedurende het hele traject een bijdrage hebben geleverd op zowel wetenschappelijk gebied als bij de morele ondersteuning. Die wil ik hier graag bedanken in mogelijk het meest gelezen hoofdstuk van een proefschrift. Allen hartelijke dank voor jullie bijdrage. Een aantal mensen wil ik in het bijzonder bedanken:

Co-promotor, **dr. J.L.C. Van Susante**: Beste Job, ik weet nog goed hoe ik tijdens mijn coassistentschap bij je op de operatiekamer stond en je aan me vroeg of ik misschien onderzoek wilde doen. Ik heb toen kort getwijfeld, maar heb er absoluut geen spijt van. Bedankt dat je me de mogelijkheid hebt geboden. Een betere begeleider en inspirator kon ik me niet wensen. Met je sterke ideeën, humor en je ongekend snelle reacties en correcties van de teksten was het een plezier om onderzoek met je te doen. Bedankt voor de mooie tijd en alle energie en tijd die je naast je werk in de onderzoeken hebt gestoken. Zonder jouw bijdrage lag dit boekje er nu niet. Naar mijn beste weten is dit het derde boekje onder jouw begeleiding wat ook een mooie prestatie is.

Promotor, **prof. dr. A. Van Kampen**: Beste Albert, bedankt voor het begeleiden van de afronding van het proefschrift en de rol die je als promotor op je wilde nemen. De afronding van het boekje heb ik dermate uitgesteld dat je middels met emiraat bent en je de coördinatie voor een groot deel vanuit je huisje in Frankrijk kon doen. Tevens wil ik je bedanken voor het vertrouwen in me tijdens de sollicitatie tot orthopedisch chirurg en de ontzettend leuke stage die ik bij je heb gelopen. Waarschijnlijk zal ik één van je laatste promovendi zijn. Ik hoop dat je van de dag geniet.

De manuscriptcommissie**:** Geachte **prof. dr. C.G.J. Sweep, prof. dr. W.M. Prokop en prof. dr. R.G.H.H. Nelissen**, hartelijk dank voor het beoordelen en goedkeuren van het manuscript. Het onbewust achterwegen laten van één van de artikelen was geen test om jullie scherpte te controleren en werd gelukkig feilloos opgemerkt.

Beste paranimfen **Bas Staffhorst** en **Jelle Schühmacher**, na een goede tijd op de middelbare school gingen we samen richting Nijmegen om te studeren. Daar bleven we elkaar regelmatig zien en hebben we de kas van menig kroeg goed gespekt. Tijdens ons (Bas) onvergetelijke bestuursjaar bij de roeivereniging werden we de twee mannen uit één stuk genoemd tussen de overige vijf vrouwelijke bestuursleden. Ik waardeer het enorm dat jullie nu, 20 jaar nadat we elkaar hebben leren kennen, mijn promotie als paranimf bijstaan. Bedankt!

Beste **Annemiek Hol**, als je als basisarts begint aan onderzoek, komt je er al snel achter dat je kennis van statistiek erg matig is. Dankzij jou wist ik binnen no time mijn statische kennis naar een acceptabel niveau te tillen. Je hield ons scherp tijdens het analyseren van de data en dankzij jou wist ik altijd zeker dat we de correcte statistische test gebruikte. Met jouw bijdrage in het coördineren van het begeleiden van patiënten en het bijhouden van de database heb je ontzettend veel werk uit handen genomen. Bedankt voor de begeleiding en alle (vrije) tijd die je in de onderzoeken hebt gestoken.

José Smolders, het duurde even voordat ik je kon opvolgen met het afronden van een boekje. Terugkijkend naar het dankwoord van jouw proefschrift kan ik hier eigenlijk de tekst kopiëren. Met jouw discipline en de snelheid waarmee je teksten op papier wist te zetten, was het erg fijn om samen met jouw artikelen te schrijven. Je hebt mij veel werk uit handen genomen waar ik je zeer dankbaar voor ben. De Bland-Altman test zal ik inderdaad niet zo snel vergeten.

Lian Roovers, als Annemiek en ik er niet uit kwamen met de statistiek stond je altijd voor ons klaar. Vooral de Bland-Altman heeft ons heel wat doen zweten. Bedankt voor je expertise.

Maarten van Gorp, Bart de Wit en de medewerkers van de afdeling radiologie in het Rijnstate Ziekenhuis, mede dankzij jullie input is hoofdstuk 6 een succes geworden met een voor ons allen onverwachte uitkomst. Jullie wisten te regelen dat de MRI's op zaterdag konden draaien en dat we de patiënten konden zien. Het waren weken waarin ik in de weekenden de afdeling radiologie vaker zag dan mijn eigen huiskamer, maar het onderzoek verliep daardoor wel snel. Maarten en Bart, bedankt voor het objectief beoordelen van alle MRI-beelden.

Mede-auteurs **Wim Schreurs, Catherine van der Straeten, Dick Zeilstra, Timothy Tan, Zhen Lu, Pat Campbell**, bedankt voor jullie medewerking bij het uitvoeren van de onderzoeken en het schrijven van de artikelen.

En niet geheel onbelangrijk, **de patiënten**, die bereid waren om mee te werken met de onderzoeken.

Miranda Dood bedankt voor het omzetten van de simpele Word teksten naar dit professioneel uitziende boekje. Als hoofdleverancier van proefschriften in de regio Oost heb je me veel werk uit handen genomen.

Stafleden van de ROGOO bedankt dat jullie me destijds hebben aangenomen voor de opleiding en de ontzettend leuke en leerzame tijd die ik nu als AIO heb.

AIOS Orthopedie van de ROGOO. Met de vele humor is het elke dag weer leuk om naar het werk te gaan. Zonder jullie was het werken zeker niet zo leuk.

Bandleden van de leukste en gezelligste coverband de BAB: Met z'n tienen hebben jullie voor een geweldige afleiding van het werk en onderzoek gezorgd. Natuurlijk was al het werk en vrijetijds-onderzoek soms wat lastig te combineren met het repeteren en optreden, maar de energie die ik van jullie en de optredens kreeg hielpen me weer verder in het onderzoek. Laten we er aankomend jaar een mooi 2^{e} lustrum van maken met nog grotere optredens. www.wijzijndebab.nl.

Beste **Cilia**, bedankt voor alle steun en interesse die je altijd in de onderzoeken hebt getoond en het begrip dat ik een enkele keer een schoonfamilieaangelegenheid moest overslaan, omdat ik weer aan het onderzoek moest werken. Joachim kan ik helaas niet meer persoonlijk bedanken, we missen hem.

Beste ouders, **Ton en Eveline**, jullie moet ik hier ook zeker bedanken. Dankzij jullie ben ik nu wie ik ben, iets waarvoor ik jullie niet genoeg voor kan bedanken. Jullie hebben me altijd vrijgelaten in mijn keuzes en gesteund tijdens mijn studie en verdere carrière, ook toen

ik besloot een jaar te stoppen met de studie of voor onderzoek naar een Sharia-gebied in Nigeria wilde afreizen. Daarnaast ben jij, Ton, als onderzoektalent ook altijd een voorbeeld voor me geweest. De grote hoeveelheid publicaties in zeer gerenommeerde tijdschriften zal ik waarschijnlijk nooit evenaren. Zal het ons nog lukken om samen een artikel te schrijven?

Lieve **Vera**, jou moet ik het meeste bedanken. Als belangrijkste persoon in mijn leven heb je het gehele promotietraject mee moeten maken, wat ook veel van jou heeft gevraagd. Toch bleef je geduldig en gunde je me alle tijd om in weekenden aan het onderzoek te werken en zorgde je op zijn tijd voor een goede afleiding. Zonder jouw steun en geduld had ik dit boekje zeker niet kunnen afronden. Nu het boekje af is zal er weer meer tijd voor elkaar zijn, die we (ons kennende) vast weer snel weten op te vullen met nieuwe hobby's en sportieve activiteiten. Met een officieel ja-woord in het vooruitzicht gaan we een mooi jaar tegemoet.

LIST OF PUBLICATIONS

1. **Bisseling P**, Bruhn J, Erdsach T, Ettema A, Bergé SJ. Long-term results of trismus release in noma patients. Int. J. Oral Maxillofac. Surg. 2010; 39(9): 873-7.

2. **Bisseling P**, Smolders JM, Hol AM, van Susante JL. No clear influence of preference bias on satisfaction and early functional outcome in resurfacing hip arthroplasty. Acta Orthop 2011; 82:161-5.

3. **Bisseling P**, Zeilstra DJ, Hol AM, van Susante JL. Metal ions levels in patients with a lumbar metal-on-metal total disc replacement: Should we be concerned? J Bone Joint Surg Br. 2011; 93:949-54.

4. Smolders JM, **Bisseling P**, Hol AM, van Susante JL. Metal ion interpretation in resurfacing versus conventional hip arthroplasty and in whole blood versus serum. How should we interpret metal ion data. Hip Int. 2011; 21(5):587-95.

5. Van de Groes S, Grinsven S, **Bisseling P**, Loon C. Totale knieprothese bij varus- en valgusdeformiteit: klinische resultaten en objectieve coronale alignement- en laxiteitmeting. Nederlands Tijdschrift voor Orthopedie 2012; 19(3): 80-7.

6. **Bisseling P**, Tan T, Lu Z, Campbell PA, Van Susante JLC. The absence of a metal on metal bearing does not exclude the formation of a destructive pseudotumor in the hip; a case report. Acta Orthop. 2013 Aug;84(4):437-41.

7. Gerhardt DMJM, **Bisseling P**, E de Visser, JL van Susante. Modular Necks in primary hip arthroplasty without anatomical deformity: No Clear Benefit on Restoration of Hip Geometry and Dislocation Rate. An exploratory study. J Arthroplasty. 2014 Aug; 29(8): 1553-8.

8. **Bisseling P**, Smolders JM, Hol A, van Susante JL. Metal ion levels and functional results following resurfacing hip arthroplasty versus conventional small-diameter metal-on-metal total hip arthroplasty; a 3 to 5year follow-up of a randomized controlled trial. J Arthroplasty. 2015 Jan;30(1):61-7.

9. **Bisseling P**, De Wit BWK, Hol A, Van Gorp MJ, Van Kampen A, van Susante JL. Similar incidence of periprosthetic fluid collections after ceramic-on-polyethylene total hip arthroplasties and metal-on-metal resurfacing arthroplasties. Bone Joint J 2015;97-B(9): 1175-82.

10. **Bisseling P,** Grinsven S, Rijnberg WJ, Loon CJ. Single system posterior stabilized revision total knee arthroplasty using a tibial tubercle osteotomy for exposure and hybrid fixation method: A minimum of 2-year follo-up analysis. Nederlands Tijdschrift voor Orthopedie 2016 mrt; 23(1): 4-10.

CURRICULUM VITAE

Pepijn Bisseling is op 21 oktober 1983 in Ede geboren. Nadat hij in 2002 het tweetalig-VWO op het Marnix College afrondt, gaat hij naar Nijmegen om daar te beginnen met zijn studie Geneeskunde aan de Radboud Universiteit. Na 3 jaar studeren onderbreekt hij zijn studie voor een jaar om fulltime aan de slag te gaan als bestuurslid van de Nijmeegse Studentenroeivereniging. Na dit jaar hervat hij zijn studie met zijn wetenschappelijke stage onder begeleiding van Prof. Bergé van de Mond- Kaak- en Aangezichtschirurgie. Voor het onderzoek reist hij af naar het noorden van Nigeria om daar vanuit het Noma Children Hospital onderzoek te doen naar de langetermijnresultaten van osteotomieën en huidtransplantaties bij kinderen die de ziekte van Noma hebben overleefd. Dit onderzoek resulteerde in zijn eerste publicatie, wat zonder enige vorm van commentaar werd geaccepteerd in een internationaal tijdschrift; iets wat hij nadien niet meer wist te evenaren. Na deze onderzoekervaring begint hij aan zijn co-schappen. De interesse voor de orthopedie ontstaat bij het co-schap orthopedie in het TweeSteden Ziekenhuis Tilburg en werd later bevestigd tijdens zijn senior co-schap orthopedie in het Rijnstate Ziekenhuis. Hier maakt hij kennis met dr. J.L.C. van Susante, die hem de mogelijkheid bood om een jaar als arts-onderzoeker aan de slag te gaan in het Rijnstate Ziekenhuis. Hier werd de basis gelegd voor dit proefschrift. Na een jaar onderzoek is hij als AGNIO aan het werk te gaan bij de orthopedie in het Rijnstate Ziekenhuis. Pepijn begint dan een jaar later met zijn (voor)opleiding tot Orthopedisch Chirurg in het RadboudUMC (dr. M.C. de Waal-Malefijt), Rijnstate (opleider dr. Rijnberg) en de Sint Maartenskliniek (opleiders dr. A.B. Wymenga en later dr. V.J.J.F. Busch), die hij naar verwachting eind 2017 zal afronden.